SIOP EDUCATION BOOK 2008

International Society of Paediatric Oncology

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Acknowledgements

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Disclaimer

The contents of this book represent the views of the individual authors and not necessarily of SIOP.
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A U T H O R S

Section A
Educational Session: State of the Art - Challenges in CNS disease

Roger J. Packer Momcilo Jankovic
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Ching-Hon Pui Michelle Monje

Section B
Keynote Lectures

A.W. Craft Nancy J. Tarbell
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CONTENTS

Authors .................................................................................................................. 7
Preface .................................................................................................................. 9

Section A - Educational Session:
State of the Art - Challenges in CNS disease

1. Leukoencephalopathy
   Momcilo Jankovic .......................................................................................... 14

2. Chemotherapy for Childhood Brain Tumors: An Update
   Roger J. Packer .............................................................................................. 20

3. Radiotherapy approaches in CNS tumours
   Beate Timmermann ..................................................................................... 26

4. Brain Tumor Stem Cells: Bringing Order to the Chaos of Brain Cancer
   Peter B. Dirks ............................................................................................... 30

5. Cranial Radiation Therapy and Damage to Hippocampal Neurogenesis
   Michelle Monje ............................................................................................ 31

6. Current Management of Central-Nervous-System Disease in Childhood Leukemia
   Ching-Hon Pui ............................................................................................. 38

Section B – Keynote lectures

1. Paediatric Oncology: The Past and the Future
   Alan W. Craft ............................................................................................... 43

2. Protons for Childhood Brain Tumors; Current Experience and Future Promise
   Nancy J. Tarbell .......................................................................................... 47

3. Liver tumours and The SIOP EL story
   Daniel C. Aronson ........................................................................................ 55

4. Medulloblastoma: Current treatment strategies and perspectives
   Stefan Rutkowski .......................................................................................... 63

5. “Trying to be a Good Parent to my Dying Child”:
   The Basis of Parental End-of-Life Decision Making in Pediatric Oncology
   Pamela S. Hinds ........................................................................................... 67
# CONTENTS

6. Non-coding RNAs in the Pathogenesis of Childhood Cancer  
   *Timothy Triche* ........................................................................................................ 72

7. New genetic insight into T-cell acute lymphoblastic leukemia  
   *Jules P.P. Meijerink* .............................................................................................. 79

8. New Horizons in Pediatric Oncology  
   *(Practical Solutions for Overcoming Professional Myopia)*  
   *Robert J. Arceci* ........................................................................................................ 83
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Preface: SIOP EDUCATION BOOK 2008

The people behind the International Society of Paediatric Oncology welcome you all here in Berlin for the 40th Annual Meeting. Together with the Scientific Committee and the Local Organizing Committee, we have created an exciting program, of which the keynote and State-of-the Art lectures are published in this SIOP Education Book 2008. We are grateful to all the presenters for their time and effort to provide us and you with these manuscripts, which can be seen as a contribution to your educational and professional development.

We have been told over and over by many of you about the value of the earlier Education Books. This feedback to our Secretariat helps us in understanding your desires and needs. We hope you will enjoy this year's book as much as the previous ones.

Maarten Egeler
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Preface: SIOP EDUCATION BOOK 2007

Welcome to the 39th Annual SIOP Congress here in Mumbai. For the third year running the keynote and State of the Art lecturers have very kindly provided papers to supplement their talks to provide delegates with a reference text for continuing profession education and development. The response from the authors has been tremendous and we are most grateful once again to them for this extra contribution to the meeting. We hope that you will all find this a very useful supplement to the meeting. Feedback on its value would be appreciated. Meanwhile on behalf of the local organisers, scientific committee and board can we wish you a very enjoyable, educating and inspiring conference?

Tim Eden
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Gabriele Calaminus
Chair Elect, Scientific Committee, SIOP
Preface: SIOP EDUCATION BOOK 2006

At each SIOP meeting we attempt to bring together many of those who are working in the field of paediatric haematology and oncology worldwide to share our experiences and our expertise. SIOP has gradually developed in recent years an increasing educational component to the meeting including specific pre-meeting educational sessions and a series of keynote lectures and state of the art talks. In 2005 we put those talks together in an educational book which we have tried to make available to those who obviously attend the meeting but also worldwide to members and those who have access to the website. I am most grateful to those who agreed to talk and present their papers that they are willing to contribute to this important educational document. We hope that those who can attend the lectures and those who can’t but are able to read this book find it useful and of course educational. The book demonstrates the wide breadth of content of current SIOP meetings. It is a good advertisement for the annual meeting. If you are reading this book and are not a member you can see why you should become one.

Enjoy the book and the talks.

Tim Eden
President, SIOP

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Chair, Scientific Committee, SIOP

Bharat Agarwal
Chair, SIOP Education Committee & Secretary General, SIOP

Pierre Wacker
Local Organizing Committee 38th Congress of SIOP
Preface: SIOP Education Book 2005

On behalf of the local organizers of the 37th Congress of the International Society of Paediatric Oncology, the Board and Scientific Committee of SIOP we would like to thank the authors for their presentations and for inclusion to this educational book along with the participants who contributed searching questions and informed comments to all of the educational sessions. This is a new venture for SIOP and is warmly welcomed by the members. Professional education is one of the key components of the SIOP meeting. We are delighted that we have had the opportunity in the wonderful surroundings of Vancouver to be able to provide an increasing component of education to the meeting. SIOP and the Education Committee have put a lot of effort into trying to create the right environment for exchange of information and knowledge. We hope that whoever reads this text will benefit from it. We planned this as an experiment this year and we hope that it will become a permanent fixture of SIOP meetings. We of course would appreciate feedback on the value of the text any comments on how we can improve the educational component of the meeting for future years. Good reading and best wishes.

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Paul Rogers
Local Organizing Committee 37th Congress of SIOP
Leukoencephalopathy

Momcilo Jankovic, Giovanna Lucchini, Antonella Colombini, Carlo De Grandi

Children affected by acute lymphoblastic leukemia (ALL) are well known to be a high risk population for central nervous system complications. As a matter of fact both patients who have and have not CNS disease involvement at diagnosis need intracranial chemotherapy. Moreover nearly 15% of newly ALL diagnosed patients are included in high risk categories for whom cranial radiotherapy is unavoidable. Both intratecal chemotherapy and cranial irradiation have been demonstrated to be risk factors for acute and chronic neurological complications and long term impairment.

The need for basal CT scan (1) and EEG evaluation in this population of patients has clearly been stated because it may be useful in case of CNS complications during the following chemotherapic treatment. From these basal studies, information about some peculiarities of these patients have been obtained. First of all ALL patients, even the ones with no CNS involvement at diagnosis exhibited anomalies both at EEG and CT scan. These anomalies seemed to be strictly correlated to the disease characteristics. Korinthenberg et al (2) showed how EEG diffuse slowing at diagnosis was strictly related to peripheral white blood cell counts, whereas Jankovic et al (3) determined that cerebral atrophy at the time of disease onset could even be a predictive factor for subsequent CNS relapse. The percentage of ALL affected children presenting with central nervous system (CNS) complications under treatment varies from 3 to 4% in literature (4,5). Among these complications leukencephalopathy (LE) surely is one of the most striking. Intrathecal methotrexate and high dose methotrexate (HD-MTX) have been advocated to play a major role in causing CNS toxicity in terms of LE, the extent of which varies from acute and reversible to irreversible and fatal. Methotrexate is a folate analog that competitively inhibits dihydrofolate reductase, inhibiting DNA, RNA, and protein synthesis. It is believed that MTX can induce direct toxic effects to the CNS by damaging the neuronal tissue. Moreover, MTX interferes with the metabolic pathways of folates, excitatory amino acids, homocysteine, S-adenosylmethionine/S-adenosylhomocysteine, adenosine and bioperterins, inducing biochemical alterations which have been associated with neurotoxic symptoms. It has been suggested that acute toxicity is partly mediated by adenosine, whereas homocysteine, S-adenosylmethionine/S-adenosylhomocysteine, excitatory amino acids and bioperterins may play an important role in the development of subacute and chronic toxicity (6). The spectrum of MTX toxicities has been described to be very wide, from acute toxicity, which is usually transient without permanent damage, to subacute and chronic toxicity which are described to be associated with changes in the brain and/or the spinal cord which may be progressive and even lead to coma and death in severe cases. In a recent and extensive review of cases Inaba et al showed that acute MTX toxicity in patients with hemato-oncologic diseases often manifests as fluctuating neurologic symptoms with alternating hemispheric involvement. Restricted diffusion on Diffusion Weighted Images (DWI) is a reliable early sign of acute MTX encephalopathy and resolves as clinical status improves, despite the persistence of subtle abnormalities on MRI (7).

Crucial to limit MTX toxicities is to understand and optimize the use of leucovorin as drug rescue and to recognize the role of cranial irradiation as important co-toxicity factor which could cause devastating cases of necrotizing LE (8). Recent studies analyzed predisposing
factors that may be involved in MTX individual response and toxicity. These elements, among which the prevalence of some genomic polymorphisms, may in future be considered as limiting factors for the administration of certain drugs (9). In particular, concerning ALL and methotrexate, recent publications have analyzed the impact of dihydrofolate reductase polymorphisms in predicting the outcome of ALL affected children treated with internationally proven protocols (10). Previous studies had shown the association of MTX neurotoxicities and dihydrofolate reductase polymorphisms in other settings of patients (11), thus leading the way to possible future information about individual predisposition not only to drug response but even to drug toxicity. To complete the possible causes of progressive CNS damage, viral infections must be cited. Being to some extent immunosuppressed, ALL patients are at higher risk for CNS viral damage, and this has been reported to occur mainly after measles infection, which is nowadays in progressive reduction (12).

It also has to be reminded that late follow up is needed to analyse the evolution of CNS complications in these patients. Pediatric oncology groups began reporting neurodevelopmental delays in children exposed to cranial-spinal irradiation in the 1980s. Halberg et al (13) showed the differences between 1800-cGy and 2400-cGy doses of prophylactic cranial irradiation on late cognitive function in children treated for ALL, with the higher doses resulting in worse function. The risk for developmental delay and learning deficits due to central nervous system (CNS) radiation therapy and chemotherapy to the CNS in ALL survivors is nowadays well documented. In details, it includes impairments in arithmetic, reading, spelling, visual motor integration, visual-spatial-organizational skills, and verbal fluency. Children who have received both radiation and intrathecal chemotherapy have shown poorer performance in tasks dependent on language function, including verbal IQ, reading and spelling, and attentional deficits. The 2 risk factors that have repeatedly shown to place ALL survivors at high risk for neurocognitive deficits include higher radiation doses and younger age at time of therapy. Moreover it has to be underlined that ALL survivors have an excess risk of morbidity and mortality linked to the increased risk of developing a second malignant neoplasm (SMN), which has been shown to be associated with irradiation. The most common SMNs in ALL survivors are malignancies of the CNS. Patients at greatest risk are those who were 5 years of age or less at the time of diagnosis and/or those who received cranial radiation (14).

In the field of LE a new issue has recently been raised. Even the so called acute reversible encephalopathy may have long term complications. The first definition of posterior reversible encephalopathy (PRES) dates back to 1996(15). At that time Hinchey described it as a reversible clinical-radiological syndrome characterized by seizure, headache, altered mental status, visual impairment and white matter oedema mainly localized in the occipital-parietal lobes. This condition could be found both in adults and paediatric patients affected by various diseases, among which cancer, autoimmune diseases, eclampsia and renal disorders. Since then, a few reports have further detailed this condition (16). From a radiological point of view it is now clear that the oedema affects the grey cerebral matter also and probably is vasogenic in origin following endothelial damage in the blood-brain barrier. Moreover, the site of pathology has been reported being not only posterior, but also involving other areas of the brain. A great number of drugs and co-morbidities have been proposed as triggering factors for the onset of the syndrome; however the role of each of them has not been well defined yet.

Since 1997, various authors have also described cases of posterior non-reversible encephalopathy, thus challenging the definition of the syndrome. In one of these latest reports, Brannon et al. described the largest paediatric series so far of patients with PRES. The cohort included 11 patients and more than half of them were found with persistent imaging and/or EEG anomalies (17).
R.L. (born 6/26/92) - All-T Intermediate Risk

During Induction phase 1A: convulsions (4/18/01) since 4/20/01; sudden blindness and full vision recovery in 1 hour.

Fig 1A: MRI fair sequence: hyperintensity areas cortical-subcortical

R.L. (born 6/26/92) - All-T Intermediate Risk

Fig 1B: MRI fair sequence: hyperintensity areas cortical-subcortical Reduction of lesions in 1 week
R.L. (born 6/26/92) - All-T Intermediate Risk

Fig 1C: MRI fair sequence: hyperintensity areas cortical-subcortical Disappearance of lesions in 1 month

Fig 2A: EEG: diffuse slowing, left occipital spikes

Fig 2B: Left occipital spikes on a normal baseline activity
The reason which underlies this clinical evolution is still to be disclosed. To check our experience in this field we reviewed the cases of PRES at our centre in the last 10 years (18). Our cohort included 12 patients. Primary diagnosis was: 9 acute lymphoblastic leukemia (ALL), 1 Fanconi anemia (FA), 1 Langherhans cell hystiocitosis (LCH), and 1 immune hemolytic anemia (IHA). At the time of PRES onset, 9 patients were undergoing chemotherapy as front-line or relapse treatment, 3 patients (1 ALL, 1 FA, 1 LCH) were at a median time of + 64 (range +36/+219) days from allogeneic hematopoietic cell transplantation (HCT), and 1 patient with IHA had been treated with monoclonal antibodies.

In 8 patients, the acute neurological event occurred with generalized epileptic or focal acute symptomatic seizures. In the case of focal symptomatic seizures, both EEG findings (occipital focal slowing, occipital epileptic status or occipital focal spikes) and clinical presenting symptoms (eye deviation, epileptic nystagmus, diplopia, elementary visual hallucinations or ictal amaurosis) indicated the involvement of occipital cortex, confirmed by neuroimaging findings at MRI (Figure 1A-1B-1C, Figure 2A-2B). In 4 patients non-epileptic confusional state occurred as neurological signs of onset. In patients with non epileptic onset, EEGs showed diffuse slowing, associated in two cases with occipital PLEDs (paroxysmal lateralized epileptic discharges). All patients showed a hyper intense T2 weighted and FLAIR image at MRI, involving both the cortical and sub cortical regions bilaterally. The localizations included occipital areas in 4 patients, frontal areas in 5 patients, parietal areas in 7 patients and temporal areas in 7 patients, in diverse combinations.

Follow-up period ranged from 10 to 124 months. All patients survived the acute event and showed a clinical recovery of the acute neurological signs in 1 to 3 days, with EEG normalizing in a period ranging from 1 to 8 months.

In long-term follow-up, 4 patients developed neurological impairment. One of these had upper right limb weakness associated with left occipital spike activity at EEG and a normal MRI; one had recurrent focal mesial temporal seizures with temporal spikes at EEG and mesial temporal sclerosis at MRI; one presented drug resistant focal and generalized seizures with a normal EEG and a pathological MRI (periventricular dystrophy, diffuse atrophy and lenticular hyper intense lesions); one exhibited persistent occipital spike activity with normal imaging findings.

In our casistics the identification of neurological signs and neuroimaging consistent with PRES in an acute setting was not enough to predict the reversibility of the pathology. As a matter of fact only a part of our patients had a complete clinical, EEG and imaging remission of the clinical picture after the neurological event. All patients, at the complete resolution of the neurological acute event, continued their therapeutic outline including, when needed, cranial RT, and intra-cranial chemotherapy.

In our series none of these elements was clearly related to a favourable or unfavourable neurological outcome.

From the imaging point of view, our experience shows that the different location of the hyperintense spotting does not correlate with a given outcome.

MRI is to be considered as the best imaging in these patients as it allows earlier diagnosis and better definition of the lesions, in details flair acquisitions help to distinguish vasogenic from cytotoxic oedema, the second being unusual in PRES lesions.

In our patients EEG proved to be an important tool for clarify the underlying mechanism of ictal events. Indeed, the recognition between the epileptic and non epileptic nature of aspecific signs as visual disturbance or altered consciousness could be achieved only through early EEG recordings.

Furthermore, serial EEG recordings resulted informative about the long term evolution of PRES. In all patients the EEG normalized in 1 to 8 months after the acute event; nevertheless after a period from 8 to 24 months some patients developed late unprovoked seizures and/or focal
spikes in the occipital region. The mechanism underlying the epileptogenesis remains to be understood.

Though there is no evidence at the present that the continuation of antiepileptic drug therapy may avoid the development of late seizures or late epilepsy after brain injury, recent data point the future identification of neuroprotective trials to prevent epileptogenesis in brain damaged patients.

We suggest that the follow-up must be continued at least for 2 years after the acute event to determine the late evolution of the PRES and the occurrence of late unprovoked seizures and to study the efficacy of neuroprotective strategies to prevent late epilepsy.

References


Chemotherapy for Childhood Brain Tumors: An Update

Roger J. Packer

Abstract

Chemotherapy, despite limitations in delivery and cellular mechanisms to develop resistance, has a definite role in the management of childhood brain tumors. Biologic treatments may play a major role in the "near" future, but have yet to be incorporated widely into treatment regimens. Reclassification of tumor subtypes may falsely inflate the reported benefit of chemotherapy; however, the use of chemotherapy has improved survival and has delayed, and in some cases, obviated the need for radiotherapy.

Introduction

Chemotherapy has taken on an increasing role in the management of childhood brain tumors. It has been used to augment the efficacy of radiotherapy to control malignant tumors and, as a means, to avoid or delay the need for radiotherapy, particularly infants and young children in whom the risk of radiation-induced toxicity is the greatest. Chemotherapy has also been effective in allowing the reduction of the dose of radiotherapy for selected patients with medulloblastoma. Some of the apparent successes of chemotherapy may be due to a reclassification of patients, with somewhat lower risk patients being randomized or stratified to adjuvant chemotherapy regimens, with the resultant false appearance of improving survival.

Drug Delivery/Resistance

Two major reasons for the lack of success of chemotherapy in selected tumor types has been chemotherapy resistance and the relative lack of drug delivery across the blood-brain barrier. [Groothius D 2000; Balis et al 2002] Strategies have been employed to overcome these limitations. High-dose chemotherapy has been utilized to increase the delivery of cytotoxic drugs to the tumor, in attempts to overcome the limited permeability of the blood-brain barrier. Initially, autologous bone marrow transplant regimens were utilized, but, more recently, studies have employed peripheral blood stem cell support. [Finlay et al 1996; Gajjar et al 2006; Guruangan et al 1998] Although this has been utilized for a variety of different tumor types, it has been shown to be most effective in infants with malignant tumors and possibly in children with medulloblastoma. The toxicity of high-dose chemotherapy supplemented by either autologous bone marrow transplant or peripheral blood cell support has remained high with a 5 to 15% death rate still being reported in series.

Biologic therapy is just being incorporated into treatment. In contradistinction to traditional chemotherapy, biologic therapy tends to be cytostatic rather than cytotoxic. This often makes evaluation of efficacy difficult. Treatments that are presently under study include: those with retinoid derivatives; gene therapy; angiogenesis inhibitors; receptor tyrosine kinase inhibitor, such as anti-EGFR and anti-PDGF small molecules; drugs which block the RAS system, such as farnesyl transferase inhibitors; mTOR inhibitors; and drugs targeting other downstream signaling pathways. [Kirsh et al 2000; Deininger et al 1997; Kuma et al 2007; Freeman et al 2006; Norden et al 2008].

Selective techniques have been utilized to try to open the blood-brain barrier. Their use has been limited and they have not shown wide-spread efficacy. [Inamura et al 1984; Emerich et al 2001; Groothius et al 2000] Another means to overcome the blood-brain barrier has been the use of lipid-soluble (often alkylating) agents, with non-overlapping hematologic toxicities.

The delivery of chemotherapy directly to the tumor, either intrathecally or intraventricularly, is...
an alternative method to increase tumor exposure. This has been utilized predominantly in attempts to control leptomeningeal disease. [Slavc et al 1998] However, to date, these methods have been limited by the lack of available active agents which can be given by this route. Also, the patient pool in pediatrics that would obtain benefit from this approach is limited. Therapy is difficult to deliver when there is altered cerebrospinal fluid circulation, especially in patients with cerebrospinal fluid shunts or partial cerebrospinal fluid obstructions. Because such therapy usually only penetrates for a few millimeters, those patients with lump disease may not benefit. Convection-enhanced intracavitary and intratumoral delivery of a radionuclide and immunotoxin-conjugated antibodies is an intriguing strategy that has not yet been widely utilized in pediatrics.

Means to overcome tumor drug-resistant has focused on two approaches. The first is the utilization of multiple drugs, and drug regimens, with different mechanisms of action and non-overlapping toxicities. A second has been to target specific chemotherapy-resistant intracellular mechanisms. For alkylators, such as CCNU and temozolomide, a major resistance mechanism is DNA alkylation repair via the enzyme AGT. [Friedman et al 1998; Friedman et al 2000] The drug, O-6-benzylguanine depletes tumor AGT levels and theoretically renders the tumor more sensitive to these alkylating agents. Unfortunately, this treatment may increase toxicity to other organs and limit the amount of drug that can be utilized.

Use of Chemotherapy for Specific Tumor Types

Medulloblastoma

Medulloblastoma is probably the tumor types for which chemotherapy has shown the greatest utility. Although adjuvant chemotherapy has never been demonstrated, in a direct randomized comparison trial, to improve survival as compared to radiation therapy alone for children with standard risk medulloblastoma, it is an accepted component of the management of patients with so-called “average-risk” (non-disseminated totally or near-totally resected) disease and high-risk disease. [Packer et al 2006; Taylor et al 2003] With post-surgery craniospinal and local boost radiotherapy alone, the best survival rates for children with medulloblastoma have been in the 60 to 65% range at five years. The addition of chemotherapy has improved this survival rate to 80 to 90%. Although preradiation chemotherapy may result in some improvement in overall disease control compared to treatment with radiation alone, the most impressive improvements in survival for children with average-risk medulloblastoma have been accomplished after treatment with chemotherapy being given during and after radiotherapy. [Kuhl et al 1998] A variety of different chemotherapeutic regimens have shown efficacy. The drug regimen utilizing vincristine during radiotherapy and cisplatin, vincristine, and either CCNU or cyclophosphamide, after radiotherapy, has resulted in survival rates as high as 85 to 90% at five years (and possibly cure). This drug regimen has also allowed the reduction of craniospinal radiation from 3600 to 2400 cGy in non-disseminated patients. [Packer et al 2006] An alternative approach utilizing similar agents at somewhat higher doses, in a truncated fashion supported by peripheral stem cell rescue, has resulted in similar overall survival rates. [Gajjar et al 2006] The utility of chemotherapy for children with average-risk disease has allowed exploration into even further reducing the dose of craniospinal radiation therapy in those children with non-disseminated disease, to doses as low as 1800 cGy. However, an important caveat to these studies is that patients have to be meticulously chosen, as those with inadequately performed staging studies or those with disseminated disease, misinterpreted on staging studies, have extremely poor survival if treatment is undertaken with reduced-dose radiotherapy.

For those children with so-called poor or high-risk medulloblastoma (those with disseminated disease or partially resected tumors), chemotherapy is also a major component of therapy. [Gajjar et al 2006] The utilization of chemotherapy during and after radiation therapy has resulted in overall survival rates in the 60 to 65% range. [Gajjar et al 2006; Kuhl et al 1998] These studies have predominantly utilized the
same agents that have been used in the average-risk studies. Alternative regimens, including the use of carboplatin during radiotherapy, are under study.

For infants with medulloblastoma, given the known neurotoxicity of craniospinal radiation, there have been multiple attempts to utilize chemotherapy to delay and, in selected cases, obviate the need for radiation therapy. [Duffner et al 1993; Geyer et al 2005] There seems to be subgroups of infants with medulloblastoma, including those with desmoplastic tumors, which seem to be more sensitive to chemotherapy and may not require radiotherapy or may require only radiotherapy to the primary tumor site after chemotherapy. Once again, a variety of different chemotherapeutic regimens have been utilized, which have included agents such as cyclophosphamide, cisplatin, vincristine and etoposide. It is unclear whether intensifications of these regimens have improved survival or whether the improving survival rates are due to a reclassification of patients; such as the removal of those children with atypical teratoid/rhabdoid tumors from the medulloblastoma classification. Recently methotrexate, both utilized intravenously, at high dose and intrathecally, has been integrated into infant medulloblastoma regimens. [Rutkowski et al 2005] Initial survival rates have been impressive, but once again seem to work best in those infants with localized, often desmoplastic tumors. Chemotherapy has not been particularly successful in controlling disease in infants with dissemination.

A major driver of all of these "apparent" improvements in outcome due to changes in drug regimens is likely patient selection. As stated previously, the separation of atypical teratoid/rhabdoid tumors from the medulloblastoma subgroup of patients has the effect of making the rate of survival seem better in studies. In addition, the inadvertent selection of better-risk patients, such as those with activation of the WNT pathway or desmoplastic tumors, may result in survival appearing better.

Other Embryonal Tumors

The efficacy of chemotherapy to enhance survival, predominantly when utilized with craniospinal and local boost radiotherapy, for other embryonal tumors, such as cortical primitive neuroectodermal tumors and pineoblastomas (actually classified as a pineal region tumor rather than an embryonal tumor) remains less proven. [Reddy et al 2000; Massisimo et al 2006; Jakacki et al 1995] The majority of patients with such tumors are treated on protocols developed for children with high-risk medulloblastomas.

A highly problematic subgroup of patients with embryonal tumors are those with atypical teratoid/rhabdoid tumors. [Packer et al 2002] Predominantly occurring in infants and young children, this tumor has been highly resistant to chemotherapy. Recent studies have either utilized chemotherapy developed for children with high-risk medulloblastoma or hybrid regimens which include "sarcoma" drugs. The efficacy of such regimens has not yet been proven. There is some early suggestion that the sarcoma regimens may be more effective, but they tend to be effective predominantly in those patients with totally resected tumor or in those old enough to receive craniospinal radiation therapy.

Low Grade Gliomas

Chemotherapy has a well-documented role in the management of infants and young children with low-grade gliomas which cannot be resected without the risk of significant morbidity. [Packer et al 1997] A variety of different combinations of therapy have been utilized in young children with low-grade gliomas, including those of the chiasm and brain stem. Probably the greatest experience has been with the use of the carboplatin and vincristine regimen. [Packer et al 1997] This regimen results in disease stabilization and/or objective responses in up to 90% of newly-diagnosed patients (two-thirds having documented disease shrinkage while on therapy) and disease control in 30 to 50% of patients five years after initiation of treatment. Other drug regimens which have been explored have been the use of vincristine, with or without other chemotherapeutic agents and an alkylator-based approach utilizing multiple different drugs. Higher dose chemotherapy utilizing drugs such as cyclophosphamide and cisplatin have also been utilized, especially in European studies, with
similar efficacy. In all of these studies, the relative toxicities of the regimens are important factors to be considered, as low-grade gliomas are often slow growing, essentially chronic conditions.

Biologic agents may play an increasing role in the management of childhood low-grade gliomas. Children with tuberous sclerosis who harbor growing giant-cell astrocytomas have been shown to benefit from treatment with mTOR inhibitors, such as rapamycin. [Franz et al 2006] Other mTOR inhibitors are in active study. In addition, patients with neurofibromatosis type 1, who have a proclivity to develop low-grade tumors (especially visual pathway gliomas) and who are at increased risk of secondary tumors and possibly vascular damage secondary to radiation, have been shown to benefit from chemotherapy. [Packer et al 1997] However, these patients are theoretically also at higher risk of mutagenesis secondary to chemotherapeutic agents, such as alkylating drugs. Thus, they also may be candidates for studies with biologic-based treatment.

High-Grade Gliomas

Although randomized studies have suggested some benefit for the addition of chemotherapy, such as CCNU or the combination of procarbazine, CCNU and vincristine, overall survival remains poor. [Finlay et al 1995; MacDonald et al 2005] In adult studies, the addition of temozolomide has improved survival for those with high-grade tumors, predominantly but not exclusively in those with methylation of the promoter of O6-alkylguanine transferase. [Stupp et al 2005] However, studies to date in pediatrics have not shown a clear benefit for the addition of temozolomide to radiation therapy for children with high-grade tumors.

At the present time, a variety of different approaches are being utilized for children with high-grade gliomas. Many have focused on the use of biologic agents either during or after radiation therapy. The combination of bevacizumab (an anti-angiogenesis agent) and irinotecan has been shown to be surprisingly effective in adults with recurrent high-grade gliomas, with response rates as high as 40 to 60% in patients with recurrent disease. [Norden et al 2008; Vriendsenburgh et al 2007] Although response has been often short-lived, these outcomes have led to studies in pediatrics utilizing these agents after radiotherapy and, in some cases, during radiotherapy. Temozolomide has also been coupled with the bevacizumab and irinotecan in attempts to prove long-term disease control.

Brain Stem Gliomas

Although a variety of chemotherapeutic agents have been used before, during and after radiotherapy for patients with brain stem gliomas, none have altered the dismal prognosis for patients with diffuse intrinsic brain stem tumors. At the present time, much of the effort is focusing on the use of drugs, be they standard chemotherapeutic agents or biologic agents, which also have radiosensitization properties. An enticing approach would be the use of local delivery systems such as convection delivered chemotherapy, or other agents, directly into the brain stem. However, convection-delivery approaches are very early in testing and there are certainly significant technical and safety considerations to overcome before they can be widely employed.

Ependymomas

The use of chemotherapy for children with ependymomas is somewhat controversial. Excellent survival rates have been reported after treatment with surgery plus local radiotherapy for children with totally resected cellular or "low-grade" ependymomas. [Merchant et al 2004] However, for children with anaplastic lesions or those which have not been totally resected, overall survival rates are not nearly as encouraging, with less than 60 to 65% of patients surviving three to five years after treatment. [Needle et al 1998; Grill et al 2001] New chemotherapeutic approaches have been predominantly aimed at those patients with partially-resected or anaplastic tumors. Chemotherapy pre-radiation drug regimens which have included cisplatin, CCNU and vincristine have been demonstrated to have a 40% or higher response rate, if utilized before radiation therapy in children with partially resected tumors, and have possibly improved survival. Other planned studies are attempting to utilize chemotherapy after radiotherapy in high-risk patients.
References


Radiotherapy approaches in CNS tumours

Beate Timmermann

Introduction

It is already quite a long time ago, when irradiation (RT) became an important part in the standard of care for CNS tumours of childhood.

Looking back, the first reports on CNS irradiation for paediatric brain tumours were published in the beginning of the last century. After combined surgery and postoperative radiotherapy survival rates of about 50% were obtained, as compared to less than 30% after surgery alone. Therefore, nearly any CNS tumour was treated with postoperative RT thereafter. RT generally used to cover the complete CNS, known as craniospinal RT. This was regardless of specific tumour histology. When chemotherapy was introduced in the treatment strategy during the 1960ies, survival rates did not increase dramatically for the majority of CNS tumours. However, by adding systemic drug therapy, intensity of RT regarding treatment volume or total dose of RT could be reduced - or start of RT could be delayed, which was desirable to reduce side effects of treatment especially in the very young.

Today, RT is still a very important tool to overcome CNS tumours in childhood. The treatment concepts vary widely to provide risk adapted intensity of treatment for each child individually. Additionally new developments in techniques have contributed significantly to minimize treatment sequelae.

Therefore, a modern risk adapted RT is an important cornerstone in the puzzle of curing any childhood CNS malignancy.

Radiotherapy approaches

CNS Target volumes

When presenting modern RT, the definition of target volume needs to be discussed. As mentioned earlier, after full CNS RT was the principal standard in the beginning of the last century, nowadays 3 different CNS target volumes can be defined: 1. craniospinal volume, 2. whole brain volume and 3. focal tumour (or tumour bed) volume.

Craniospinal irradiation (CSI)

The craniospinal volume covers all leptomeningeal areas. Usually at the cranial side, it includes the skull, the cerebrum and cerebellum. The skull base serves as the ventral border. Below, all spinal canal is covered down to S2. Today, craniospinal RT is performed only for some few tumours carrying high risk for leptomeningeal dissemination, e.g. supratentorial PNETs. Additionally it is routinely performed when dissemination within the CNS is already present.

Whole brain irradiation (WBI)

The treatment field covers the entire intracranial, leptomeningeal volume down to C2 (see cranial part of CSI). Today, it is performed for selected children with leukaemia or for palliation in case of brain metastases.

Focal tumour irradiation

This is the most frequent way of treating children with CNS tumours today. In principal either the tumour or the postoperative surgery bed is covered with an additional safety margin for potential subclinical extension. The safety margin depends on the tumour histology and the surgical performance. This approach is typically used for tumours with a low risk for leptomeningeal spread or when systemic treatment is likely to prevent CNS dissemination successfully. Examples for indications are non-metastatic ependymomas and gliomas.
Concepts for the most common brain tumours

Low grade glioma (LGG)

The low grade glioma is the most frequent tumour of the CNS in childhood. It typically arises from the optical pathway. Since the experiences from the LLG trials in Germany, Europe and US, there are several options to proceed when a LGG is diagnosed. Usually according to age, tumour evolution and site of tumour, either watchful waiting, or surgery, chemotherapy or radiotherapy can be performed. Frequently during the full history of disease, combination of those options was chosen. In Europe and Germany the SIOP-LGG 2000 trial is active for patient accrual (web-info: www.kinderkrebsinfo.de, e-mail: gnekow.hit-lgg@klinikum-augsburg.de)

In case of irradiation, usually local RT is administered. Safety margins around the visible tumour are sized 5-10 mm routinely. Total doses usually are between 45 and 54.0 Gy, with 1.8 Gy dose per fraction.

It is well known, that after RT, asymptomatic changes in MRI are frequently occurring in LGG patients (or less frequently symptomatic). Sometimes even necrosis can be observed.

Local control rates of about 75% can be achieved after RT.

High grade glioma (HGG)

High grade gliomas still comprise a group of tumours with very unfavourable prognosis. Even after introducing aggressive chemotherapy and dose escalation of RT (up to nearly 80 Gy using hyperfractionated regimens), outcome still remains unsatisfactory with about 20% overall survival rate. The tumour unfortunately tends to infiltrate extensively subclinically in the surrounding tissue.

As the standard of care, local irradiation with total dose of 54-60 Gy is performed in all children with HGG. A safety margin of 15-20 mm around the tumour (bed) should be introduced, covering all oedema in the neighbourhood of the tumour.

In Germany, the HIT-HGG D study is open to accrue patients for combined chemotherapy and irradiation (web-info: www.kinderkrebsinfo.de, e-mail: christofkramm@hotmail.de).

Medulloblastoma (MB)

The medulloblastoma is the most common infratentorial tumour in childhood. In some countries the medulloblastoma is better known as infratentorial primitive neuroectodermal tumour (PNET). In Germany the children with MB are treated according to the HIT-2000(MB) trial with chemotherapy and additionally RT if older than 4 years of age (web: www.kinderkrebsinfo.de, e-mail: rutkowski_s@klinik.uni-wuerzburg.de). The medulloblastoma was reported to spread frequently via the cerebrospinal fluid. Therefore any MB was treated with craniospinal axis irradiation for many years. Since some years, study groups are investigating if local RT is sufficient for very young children and for low risk MB. Results are promising and consequently in selected subgroups of the MB patients, CSI may be avoidable.

Still, treatment standard comprises CSI of 24-36 Gy with an additional boost to the tumour volume (bed) to a cumulative dose of 54 Gy.

Supratentorial primitive neuroectodermal tumour (stPNET)

The stPNET is the supratentorial counterpart of the MB. Even if the histology implies a close relation between the MB and the stPNET, the stPNET behaves much more aggressive and, consequently survival rates are significantly inferior. According to the high risk of failure, the treatment concept implies that aggressive radiotherapy is added to an aggressive chemotherapy. Full CNS irradiation with an additional boost to the tumour is recommended for any stPNET. Total dose of the CSI is 36-40 Gy and a tumour dose of 54-60 Gy is prescribed.

The patients are enrolled in the protocol HIT2000(stPNET) in Germany (web: www.kinderkrebsinfo.de, e-mail: rutkowski_s@klinik.uni-wuerzburg.de).

Ependymoma

Ependymomas can arise from the supratentorial or infratentorial brain. Infrequently also spinal tumour sites are observed. Typically any failure is involving the primary tumour site. Therefore, local treatment procedures are the most important contributors to any cure. Complete
tumour resection is recommended whenever possible. Even second look surgery might be considered during the course of treatment. The role of chemotherapy is not yet proven. Therefore its use is restricted to trials or recurrent ependymomas.

Radiotherapy has a proven role for ependymomas. Even dose escalation seems to be justified, at least in residual tumours. Today, local therapy of 60 Gy for non-residual tumour is mandatory. For residual tumour second look surgery or stereotactic boost should be considered. In Germany patients are enrolled in the HIT 2000(Ep) trial (web: www.kinderkrebsinfo.de, e-mail: rutkowski_s@klinik.uni-wuerzburg.de).

Craniopharyngeoma

The craniopharyngeoma arises in the sellar region. The tumour site implies multiple problems for treatment and disease or treatment related sequelae. Typically the tumour consists of solid and cystic parts. In principal surgical and/or radiotherapeutic procedures can be performed. Some publications suggest to go for limited surgery followed by local RT to obtain better QoL result. Still, many children are primarily operated on their tumour. In principal also definite RT alone is an option. However, any RT is performed with local field treatment including the tumour and an additional safety margin for the CTV of about 5mm to 50.4-54 Gy. It should be noted, that RT in craniopharyngeomas is not trivial. Changes in shape or size of the tumour during RT course frequently occur. Therefore, repeated CT scanning during irradiation course is suggested. Infiltration is not of great concern usually. Therefore, very little safety margins are used suggesting a role for high-precision RT like stereotactical RT, proton therapy etc.

In Germany, all children are observed or treated according to the Kraniopharyngeom 2007-Protocol (web-info: www.kinderkrebsinfo.de. E-Mail: kikra.doku@klinikum-oldenburg.de ).

Concepts for spinal tumours

Spinal tumours in childhood are rare. Some paediatric ependymomas and gliomas may arise in the spinal canal. As a general concept, surgery usually is the first choice of treatment, if resectable. In unresectable or incompletely resected tumours radiotherapy is an option. However, the limited tolerance of the spinal cord makes it difficult to administer doses over 50 Gy to this site. To avoid asymmetric growth and consequently scoliosis or lordosis, coverage of the complete vertebral body should be considered.

Side effects of CNS irradiation

Whenever focussing on treatment concepts in childhood malignancies today, the risk for adverse side effects have to be taken into account. Each treatment modality carries its typical risks. The quality of life after tumour cure is the summary of all adverse side effects from all modalities. After cure rates in paediatric oncology have increased considerably during the past decades, the QoL after cure is of major interest today.

Unfortunately, any child suffering from a CNS tumour is prone to experience severe adverse late effects. Regarding RT, the extent of side effects is depending on dose of RT, volume of RT and age at time of RT. Unfortunately the median age of the brain tumour patients is considerably low with about 3-5 years.

The list of possible side effects is long and comprises a full scope of serious impairments affecting quality of life significantly: Decline of intelligence, neurological deficits, hearing impairment, growth retardation, endocrinology dysfunction of pituitary or thyroid, psycho-social problems and last but not least increased incidence of secondary malignancies (SMN).

Therefore it is obvious, that especially in the very young patients, treatment strategies aim to delay RT and decrease doses of RT or limit the target volume.

Innovative techniques in CNS iradiation

In general 3-D conformal RT after CT planning and careful immobilisation procedures is the standard RT for paediatric brain tumours. Still, innovations in RT techniques are increasingly used and obviously their benefit is investigated exactly in the group of patients prone to severe side effects as the CNS tumour cohort.
Stereotactical Radiotherapy (SRT)
This technique either performed as single fraction RT (radiosurgery) or as fractionated SRT provides excellent conformality due to multiple field arrangement and a steep dose fall-off at the border of the target. It requires precise and often also rigid immobilisation. It is used for small, regular targets in near vicinity to organs at risk and when high doses are required. It is routinely performed in centers for patients with recurrent CNS tumours, meningiomas, craniopharyngeomas or selected LGG of the optical pathway. In Europe SRT will be part of the RT protocol for ependymomas with residual disease. Lately, the "Cyberknife" offers SRT also for extracranial sites without the necessity for rigid immobilisation.

Intensity modulated radiotherapy (IMRT)
By combining multiple, individually optimized fields, high conformality is achieved. However, clinical data is sparse and spreading low- and medium dose potentially increases the risk for SMN. Therefore it is not considered as the standard, even if it may be used for better sparing of organs at risk in some cases.

Tomotherapy
Tomotherapy combines IMRT and image guided RT. Due to hundreds of fields, the irradiated volume is large and, therefore also carrying potential risk for SMN induction. Clinical data on paediatric patients is not available so far. Still, craniospinal tomotherapy of the whole CNS might be a good alternative to conventional techniques and will be interesting to investigate in the future.

Proton Therapy
PT offers high conformity without the need for multiple field arrangements. Distal to the target the dose fall-off is very steep due to the particle physics. Therefore it is highly conformal without increasing the theoretical risk for SMN. Even though patients are treated with PT for more than 50 years now, clinical data about late effects is rare. Cost of treatment is high and treatment slots are limited, especially in Europe. Still, increasing use for paediatric CNS treatments has to be expected in the near future.

Summary and Conclusion
Radiotherapy still plays a major role in the multidisciplinary standard of care for CNS tumours in childhood today. Due to individually risk adapted concepts and technical improvements, RT can contribute considerably to minimize adverse effects in the majority of children. Additionally, improved conformality of modern RT allows to escalate RT dose in high risk situations when dose response relationship has been proven.
Brain tumor Stem Cells: Bringing order to the Chaos of Brain Cancer

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Peter B. Dirks
Cranial radiation therapy is a crucial modality in the treatment of central nervous system malignancies. Unfortunately, cranial radiotherapy is frequently associated with a progressive decline in cognitive function, prominently memory function, in both children and adults. Classically, radiation-induced neurological injury has been attributed to vascular damage and demyelination. However, cognitive impairment is often present in the absence of overt structural changes, indicating that a more subtle physiological process may be affected. New neuron addition in the postnatal hippocampus is one such process. Impairment of hippocampal neurogenesis following therapeutic doses of radiation has now been demonstrated in animal models and in human subjects, and is thought to be an important mechanism underlying radiation-induced cognitive decline. Recent work has elucidated the mechanisms of radiation-induced failure of neurogenesis. Potential therapeutic interventions are emerging.

Introduction

Cognitive dysfunction, characterized by prominent impairment of short-term memory, is perhaps the most common sequelae of radiotherapy. Cranial radiotherapy causes a debilitating cognitive decline in both children (Roman and Sperduto, 1995) (Anderson et al., 2000) (Moore, Ill et al., 1992) and adults (Crossen et al., 1994) (Abayomi, 1996) (Lee et al., 1989) (Surma-aho et al., 2001) (Kramer et al., 1997). Months to years after cranial radiation exposure, patients exhibit progressive deficits in memory, spatial relations, visual motor processing, quantitative skills and attention (strother, 2002). Hippocampal dysfunction is a prominent feature of these neuropsychological sequelae. In fact, the severity of the cognitive deterioration appears to depend upon the radiation dosage delivered to the medial temporal lobes (Abayomi, 2002). The incidence of treatment-induced impairment in cognition has been very well described in children. It is estimated that, when irradiated at age less than 7 year, nearly 100% of children require special education; after 7 years of age approximately 50% of children require special education. Some degree of memory dysfunction is thought to occur in the majority of children. The incidence of memory impairment in adult patients has been difficult to quantify, largely due to a lack of uniformity in neuropsychometric testing in the literature. However, as adults are surviving longer after treatment and the long-term consequences of radiation are becoming more important for this population, an extremely high rate of cognitive dysfunction of varying degrees has been recognized, with frank dementia affecting as many as 12% of patients (Crossen et al., 1994).

Severe cognitive dysfunction may be associated with treatment-induced leukoencephalopathy and/or radiation necrosis. However, mild to moderate cognitive dysfunction is inconsistently associated with radiological findings, and frequently occurs in patients with normal-appearing neuroimaging (Dropcho, 1991). Clinically significant memory deficits in the absence of radiological findings implicates damage to a subtle process with robust physiological consequences.

Hippocampal progenitors in the post-natal brain

Hippocampal neurogenesis is one such physiological process. Located in the medial temporal lobes, the hippocampal formation plays a central role in learning and memory (Squire, 1993; Zola-Morgan and Squire, 1993) - functions prominently affected by radiation. Neural stem cells, self-renewing cells that generate neurons, astroglia and oligodendroglia, as well as lineage-restricted neural precursor
cells, exist in the postnatal and adult brains of all mammals studied to date, including humans (Eriksson et al., 1998) (Zhao et al., 2008). Neural stem cells, neuronal precursor cells and glial precursor cells are collectively known as neural progenitor cells (NPCs). In the hippocampus, a major site of postnatal/adult neurogenesis, NPCs generate newborn dentate gyrus granule cell neurons throughout life. These newborn hippocampal granule cell neurons migrate into the granule cell layer proper, integrate and become electrophysiologically functional (Markakis and Gage, 1999) (Hastings and Gould, 1999) (van et al., 2002). While the electrophysiological properties of the mature newborn neuron (approximately 4 weeks after new neuron generation) are identical to those of the established granule cell neurons, electrophysiological properties of the immature newborn neuron (1 - 3 weeks old) are distinct and therefore possess particularly powerful capabilities to alter the performance of a circuit (Ge et al., 2007).

New neuron generation is believed to be crucial for certain types of memory function. In rodents, increased hippocampal neurogenesis results in improved performance in certain hippocampal-dependent memory tasks (van et al., 1999). Neurogenesis is increased by voluntary physical exercise (van et al., 1999), exposure to an enriched environment (Kempermann et al., 1997) and by hippocampal-dependent learning (Leuner et al., 2006). The mechanism by which cognitive challenges increase neurogenesis appears to be mediated by increased activity flow through the hippocampal circuit (Deisseroth et al., 2004) (Airan et al., 2007). In this way, use of the hippocampal circuit, at the right time and in the right way, strengthens the circuit, much as weight lifting strengthens muscles.

Conversely, disruption of hippocampal neurogenesis generally results in decreased performance in certain hippocampal-dependent memory tasks, such as finding the way out of a maze (Shors et al., 2001) (Cameron and Gould, 1994) (Lemaire et al., 2000) (Madsen et al., 2003) (Raber et al., 2004) (Rola et al., 2004). Several exogenous and endogenous conditions negatively regulate neurogenesis in the hippocampus, including chemotherapy (Shors et al., 2001), radiation therapy (Parent et al., 1999) (Monje et al., 2002), the glucocorticoid stress hormones (Mirescu and Gould, 2006) and certain inflammatory states (Monje et al., 2003b) (Ekdahl et al., 2003). Cranial radiation has repeatedly shown to cause defects in hippocampal-dependent behavioral tests in rodents (Rola et al., 2004) (Raber et al., 2004) (Madsen et al., 2003).

It should be noted that experiments designed to test the effects of reduced neurogenesis on cognition have been limited to date by lack of techniques to specifically block postnatal neurogenesis without affecting any other cell type. All current interventions to reduce neurogenesis have pleiotropic effects; for example irradiation inhibits production not only of new neurons, but also of new glial cells (albeit to a lesser extent) and furthermore causes damage to existing cell types. Definitive studies to demonstrate that neurogenesis plays a key role in cognition will require the development of an animal model in which selective control of postnatal neurogenesis alone is possible. It is also the case that hippocampal neurogenesis is important for some, but not all, forms of hippocampal-dependent memory function (Zhao et al., 2008). This may explain conflicting animal study results (Raber et al., 2004) (Rola et al., 2004) and highlights that testing the role of hippocampal neurogenesis in animal models must be performed accordingly. That said, the weight of available correlative data indicates that neurogenesis plays a significant role in normal memory function.

Ongoing hippocampal neurogenesis is likely important for human cognition as well; while experimental manipulation of neurogenesis in humans is not ethically possible, conditions known to alter neurogenesis for better or worse, such as voluntary physical exercise or aging, are associated with corresponding changes in memory function in humans (Angevaren et al., 2008).

Microenvironmental determinants of neurogenesis

The process of neurogenesis requires a specific neurogenic microenvironment, referred to as the neurogenic niche. Transplantation experiments demonstrate that neurogenesis is restricted in
the postnatal brain to regions in which it occurs naturally, namely the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus (Suhonen et al., 1996) (Luskin, 1998). Microenvironmental determinants of neurogenesis include the presence of the trophic signals required for progenitor cell proliferation, differentiation and survival, and the absence of inhibitory factors. NPCs form a close anatomical relationship with the microvasculature in the neurogenic region, and this neurovascular relationship is believed to be crucial not only for nutritional but also for trophic support (Palmer et al., 2000). Hippocampal astrocytes cells play key roles in creating and maintaining the neurogenic niche (Song et al., 2002). Many of the canonical signaling pathways central to prenatal neural development are conserved in postnatal neurogenesis, including Wnt, Shh, and Notch (Lie et al., 2005) (Ahn and Joyner, 2005; Breunig et al., 2007). Additional molecules with potent pro-neurogenic effects include fibroblast growth factor (FGF) (Gage et al., 1995), vascular endothelial growth factor (VEGF) (Fabel et al., 2003) and certain neurotransmitters (Cameron et al., 1995).

An important negative regulator of the neurogenic microenvironment is microglial inflammation, particularly in disease states. Pro-inflammatory cytokines elaborated by microglial cells in certain states of activation, including IL-6 and TNF-alpha, inhibit neurogenesis via a specific blockade in neuronal differentiation, as well as no-specific increase in precursor cell death (Monje et al., 2002). The effects of inflammatory cells on neurogenesis are complex and depend on the microglial phenotype involved; microglia stimulated by cranial irradiation or systemically-administered lipopolysaccaride (LPS, also known as endotoxin) inhibit neurogenesis (Monje et al., 2003b), while microglia stimulated by IL-4 or interferon gamma promote neurogenesis (Butovsky et al., 2006)

**Radiation effects on hippocampal neurogenesis**

Work in animal models of cranial radiation therapy have elucidated the pathologic effect of radiation on hippocampal progenitor cell biology. In typical models, a single dose of ionizing radiation, a rodent equivalent of what a human would receive in one day's radiation treatment, is administered to the cranium while protecting the eyes, ears and snout. At the same time, a marker of dividing cells (usually the thymidine analogue bromo-deoxyuridine) is administered to the animal. Thus, one is able to indelibly label and track the fate of all cells proliferating at the time of radiation exposure. Such work has demonstrated that exposure to therapeutic doses of irradiation results in an increase in apoptosis (Tada et al., 2000) (Peissner et al., 1999) (Yazlovitskaya EM et al., 2006), a decrease in cell proliferation and a decrease in the neuronal differentiation in the neurogenic region of the hippocampus (Parent et al., 1999) (Monje et al., 2002) (Tada et al., 2000) (Snyder et al., 2001). A thorough analysis that accounted for both the decrease in the proportion of dividing cells that successfully form newborn neurons and the decrease in overall cell proliferation within the neurogenic region revealed a 97% decrease in absolute neuron production throughout the entire volume of the hippocampus two months following a single clinically-relevant dose of radiation (Monje et al., 2002). Neurogenesis is essentially ablated.

The deficit in cell proliferation could simply be due to annihilation of the NPC pool. Alternatively, the precursors may survive radiation, but have limited growth potential due either to cell intrinsic damage or to lack of extrinsic mitogenic signals. The direct isolation of equivalent numbers of NPCs from hippocampi one month after exposure to 0, 2 or 10 Gy X-irradiation clearly demonstrated that an acute ablation of the NPC population does not occur (Monje et al., 2002). However, those NPCs exhibited impaired growth potential in a radiation dose-dependent manner (Monje et al., 2002), with delayed in vitro growth of NPCs isolated from brains exposed to 2 Gy and failure of NPCs isolated from brains exposed to 10 Gy to expand in vitro, possibly because of radiation-induced DNA damage and subsequent mitotic catastrophe. Thus, the striking decrease in proliferating cells within the neurogenic region in the months following radiation exposure probably results from both acute cell death and impaired proliferative potential of the precursor pool. What was observed in vitro, where cells divide very rapidly due to lack of contact
inhibition and strong mitogenic signals in the growth medium, is likely an accelerated version of what occurs in vivo. One would infer that, over time, the hippocampal precursor population may become depleted. It is clear, however, that NPCs are present in ample numbers at early time points, yet do not produce new neurons.

In contrast to neurogenesis, gliogenesis is relatively preserved following irradiation (Monje et al., 2002). The disproportionate deficit in neurogenesis is could be due to a stem cell-intrinsic defect, or could be due to a failure of the neurogenic microenvironment. To test the intrinsic ability of the irradiated NPC to make a neuron, NPCs were isolated from rat brains exposed to either 0, 2 or 10 Gy and allowed to differentiate in the Petri dish - away from the local environment of the irradiated hippocampus. These NPCs from irradiated brains could make neurons, and in fact did so in the same neuron:glia ratio as non-irradiated NPCs (Monje et al., 2002).

Irradiated NPCs do retain the ability to make neurons, but do not do so in vivo. This suggests that the microenvironment of the irradiated hippocampus may be to blame (in part) for the near complete absence of neurogenesis. To probe the integrity of the neurogenic microenvironment following irradiation, healthy, non-irradiated NPCs were transplanted into the irradiated hippocampus. These non-irradiated NPCs similarly failed to make neurons (Monje et al., 2002), indicating that radiation damages the microenvironment necessary for neurogenesis.

Two prominent alterations in the neurogenic niche have been noted in the irradiated hippocampus. First, there is a disruption of the neurovascular niche such that the NPCs no longer cluster around the neurovasculature (Monje et al., 2002). Second, radiation causes a striking microglial inflammatory response (Monje et al., 2002) (Monje et al., 2003b). This finding is intriguing, as microglial inflammation and subsequent elaboration of pro-inflammatory cytokines inhibit neurogenesis (Monje et al., 2003b; Mizumatsu et al., 2003) (Ekdahl et al., 2003). Furthermore, neuroinflammation alone is sufficient to cause disruption of the neurovascular relationship (Monje et al., 2003b), and treatment with an anti-inflammatory agent restores both the microanatomical relationship of NPCs with microvasculature in the neurogenic region and neurogenesis following systemic inflammatory challenge with LPS (Monje et al., 2003b).

Restoring the neurogenic microenvironment

A simple anti-inflammatory strategy has proven successful in improving neurogenesis in a rat model of cranial radiation therapy. The non-steroidal agent indomethacin, which functions as a cyclo-oxygenase (COX) I and II inhibitor, as well as a direct peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist, was administered in a clinically-relevant dose during and after cranial radiation exposure. Indomethacin administration during and after irradiation resulted in a 35% decrease in activated microglia within the neurogenic region of the hippocampus and a 250% increase in the absolute number of newly generated neurons relative to animals irradiated without anti-inflammatory intervention (Monje et al., 2003b). While this represents a great improvement, this strategy alone did not restore neurogenesis to baseline levels and the effect on hippocampal function remains to be seen. More potent anti-inflammatory/anti-microglial agents may confer a greater benefit to hippocampal neurogenesis, and experiments are undoubtedly ongoing to identify the most efficacious agent. One should note that glucocorticoids, often used to control lymphocytic neuroinflammation, are not a useful class of agents to consider, as glucocorticoids severely decrease neurogenesis via independent mechanisms.

Human neurogenesis following treatment for CNS malignancies

Recent work has confirmed the above animal model findings in patients following treatment for central nervous system malignancies (Monje et al., 2007). Post-mortem analysis of hippocampal neurogenesis in three patients with medulloblastoma (two children and one adult) and one infant with acute myelogenous leukemia (AML) that involved the central nervous system and who had undergone a bone marrow transplant were evaluated using the newborn neuron-specific marker doublecortin. Compared
to age and sex-matched control subjects who had died from non-neurological and non-oncological causes, the patients who had received treatment for medulloblastoma exhibited a 10-fold decrease in neurogenesis. These subjects with medulloblastoma were evaluated at time points ranging from 2 - 23 years after the completion of radiotherapy. The infant with AML exhibited a 100-fold decrease in neurogenesis relative to an age and sex-matched control subject. These findings clearly illustrate the long-lasting damage to hippocampal neurogenesis caused by the cumulative effects of treatment, including cranial irradiation, chemotherapy, glucocorticoid therapy for cerebral edema, and perhaps endogenous factors related to the disease process itself.

One of the cases studied, however, offered a unique opportunity to examine the effects of radiotherapy alone. A patient with medulloblastoma, a seven year old female, suffered a unilateral recurrence of her tumor adjacent to, but not invading, the left hippocampus. She therefore received additional focal radiotherapy to the left hippocampus. The right hippocampus thus served as an internal control for systemic factors such as chemotherapy. Relative to the right hippocampus, the irradiated left hippocampus exhibited a 79% reduction in neurogenesis, a 59% reduction in overall cell proliferation within the neurogenic region, a 200% increase in activated microglia and relative preservation of gliogenesis (Monje et al., 2007). These findings mirror those from the rodent model of radiotherapy and confirm ablation of human neurogenesis following cranial radiation therapy.

Conclusions and potential therapeutic avenues

Cranial radiation therapy causes profound inhibition of hippocampal neurogenesis in both animal models and in humans. Given the tremendous numbers of new neurons generated in a normal individual and their unique role in hippocampal function, it is not difficult to extrapolate that the absence of this endogenous repair or plasticity mechanism would contribute to a progressive decline in memory function like that seen in survivors of central nervous system malignancies. Cranial radiation therapy affects hippocampal neurogenesis in at least two important ways. First, radiation-induced damage to NPCs impairs growth potential and likely affects the progenitor pool in the long-term. Second, radiation-induced perturbation of the neurogenic microenvironment prevents the remaining NPCs from forming new neurons. An important microenvironmental change is a prominent microglial inflammatory response, seen in both rodents and humans following radiation exposure. Activated microglia inhibit neurogenesis, and in rodents a simple non-steroidal anti-inflammatory strategy partially restores neurogenesis. Whether anti-inflammatory therapy administered during and after radiation therapy would be similarly beneficial in humans remains to be explored. It is possible that anti-inflammatory therapy may improve memory function following radiation therapy. However, additional preclinical safety data is needed to ensure that calming the microglial response does not adversely affect tumor treatment efficacy. It is also important to consider the combinatorial effects of CNS tumor treatment strategies that include not only radiation but also glucocorticoids like dexamethasone and chemotherapeutic agents; the cumulative effects of these multiple neurogenic insults may not be easy to overcome and will likely require a multi-pronged approach to return hippocampal neurogenesis to normal or near-normal levels. Finally, addressing the radiation-induced damage to NPC growth potential will require treatments that could include neuroprotective (Yazlovitskaya EM et al., 2006) and/or cell replacement strategies. Repairing the neurogenic microenvironment is fundamental to the success of any therapeutic intervention, as neither the recruitment of endogenous NPCs nor stem cell transplantation would be possible without an intact neurogenic microenvironment.

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Abstract
Control of central-nervous-system leukemia (CNS) remains a therapeutic challenge in childhood acute lymphoblastic leukemia (ALL), and may emerge as a therapeutic concern as systemic control improves in childhood acute myeloid leukemia (AML). To avoid acute and late complications associated with cranial irradiation, this treatment modality is now reserved for 2% to 20% of patients with ALL at particularly high risk of CNS relapse (such as T-cell ALL with initial leukocyte count of $\geq 100 \times 10^9/L$, high-risk genetic features, over CNS leukemia at diagnosis or poor response to remission induction therapy), and for approximately 2% of AML cases with overt CNS leukemia at diagnosis. Ongoing studies are testing if intensive intrathecal and systemic therapy can eliminate the use of cranial irradiation for all patients with newly diagnosed leukemia. With current therapy, approximately 3% to 8% of patients can be expected to develop CNS relapse. While children with B-cell precursor ALL who have a late CNS relapse and did not receive cranial irradiation have an excellent outcome after retrieval therapy, innovative treatment options are needed for those with CNS relapse after a short initial remission or cranial irradiation.

Introduction
Contemporary risk-directed treatment have improved the 5-year event-free survival rates for childhood acute lymphoblastic leukemia (ALL) to 80% or more and for acute myeloid leukemia (AML) to 50% or more. Despite these advances, central-nervous-system (CNS) relapse still occurs in 3% to 8% of children with either ALL or AML, and remains a major therapeutic obstacle to cure, especially for ALL (Pui & Howard, 2008). The relatively high rates of CNS relapse can be attributed partly to improved hematologic control and partly to the decreased use of cranial irradiation to avoid long-term sequelae. Indeed, attempts have been made to eliminate or reduce the dose of CNS irradiation even in patients with CNS leukemia at diagnosis or relapse. To this end, most protocols do not specify cranial irradiation for infants or very young children, regardless of their presenting features. To further improve the cure rates, more effective CNS-directed therapy is necessary. Current strategies of CNS-directed therapy and some of the challenges will be addressed here.

Risk Factors for CNS Relapse
Factors associated with an increased risk of CNS relapse in ALL include a T-cell phenotype, high initial leukocyte count, adverse genetic abnormalities (e.g., Philadelphia chromosome, the t(4;11) with MLL-AF4 fusion), and the presence of leukemic cells in cerebrospinal fluid (i.e., CNS2, CNS3 and traumatic lumbar puncture with blasts) (Pui & Howard, 2008). In our recently completed Total Therapy Study XV with an event-free survival of 86%±4% and isolated CNS relapse rate of 3%±1% at 5 years, the presence of blasts in cerebrospinal fluid and T-cell phenotype were the two independent factors associated with an increased risk of CNS relapse (hazard ratios, 8.5 and 4.5, respectively; Pui et al. unpublished data). Among B-lineage ALL, pre-B ALL with t(1;19) and E2A-PBX1 fusion has the highest risk of CNS relapse. Polymorphisms in genes that code for proteins involved in the pharmacodynamics of antileukemic drugs such as vitamin D receptor and thymidylate synthetase may also be associated with an increased risk of CNS relapse (Rocha et al., 2005). Interestingly, a recent study suggested that high expression of interleukin-15 in diagnostic leukemic cells was associated with CNS leukemia at diagnosis and subsequent CNS relapse, suggesting a pathogenetic role of this cytokine in leukemic cell migration into the CNS (Cairo et al., 2007).
In AML, monoblastic or myelomonoblastic leukemia, chromosome 11 abnormalities, young age (<2 years), high leukocyte count, hepatosplenomegaly, and CNS leukemia at diagnosis have been associated with an increased risk of CNS relapse (Pui & Howard, 2008).

**CNS-directed Therapy for Newly Diagnosed Patients**

**Cranial irradiation**

Because of its association with many acute and late complications, cranial irradiation is now reserved for only 2% to 20% of patients at very high risk of CNS relapse in ALL (Pui & Howard, 2008). Investigators of the Berlin-Frankfurt-Münster (BFM) group showed that the radiation dose can be lowered to 12 Gy for most patients and to 18 Gy for those with CNS3 status. Investigators of the European Organisation for Research and Treatment of Cancer and St. Jude Children’s Research Hospital omit cranial irradiation in all patients and reserve it for salvage therapy. This strategy is based not only on an expected low rate of CNS relapse, but also on a high retrieval rate for patients with an isolated CNS relapse who have not received cranial irradiation as initial CNS-directed therapy. In AML, cranial irradiation is generally not used or is used only in patients with CNS3 status.

**Intrathecal therapy**

Three anticancer drugs—methotrexate, cytarabine and glucocorticoids (usually hydrocortisone), and various combinations of these agents — are routinely administered by the intrathecal route to patients with leukemia. Intrathecal methotrexate, dosed by age rather than body surface area, has been standard therapy in most studies of ALL. Investigators of the European Organisation for Research and Treatment of Cancer and St. Jude Children’s Research Hospital omit cranial irradiation in all patients and reserve it for salvage therapy. This strategy is based not only on an expected low rate of CNS relapse, but also on a high retrieval rate for patients with an isolated CNS relapse who have not received cranial irradiation as initial CNS-directed therapy. In AML, cranial irradiation is generally not used or is used only in patients with CNS3 status.

One explanation for this seemingly paradoxical finding is that an “isolated” CNS relapse may in fact be an early manifestation of systemic relapse, and that the better CNS control secured with triple intrathecal therapy versus intrathecal methotrexate favors overt leukemic relapse in other sites at a later time. Thus, more effective systemic chemotherapy will be needed before the full benefit of triple intrathecal therapy can be realized.

In AML, cytarabine has been the preferred drug for intrathecal therapy, perhaps because it is more effective than methotrexate for systemic therapy. However, there have been no randomized trials to test the efficacy of different regimens of intrathecal therapy. In some studies, adequate CNS control was attained with intrathecal methotrexate alone (Pui & Howard, 2008). Triple intrathecal therapy was used in two previous St. Jude clinical studies, in which none of the 131 patients experienced a CNS relapse. In the most recent St. Jude study, intrathecal cytarabine was first used as CNS-directed therapy. Of the first 28 patients treated, 3 developed an isolated CNS relapse, prompting protocol amendment to revert to the use of triple intrathecal therapy (Rubnitz et al. unpublished observation). Of the subsequent 164 patients treated, none developed CNS relapse. Low rates of CNS relapse were also observed in several other studies using triple intrathecal therapy (Pui & Howard, 2008). Future testing of the relative efficacy of triple intrathecal therapy versus intrathecal cytarabine is warranted in children with AML.

Cytotoxic concentrations of intrathecal chemotherapy are maintained in the CSF for a relatively short time, and performing frequent lumbar punctures in some patients presents technical difficulties. Thus, liposomal cytarabine (DepoCyt®, Enzon Pharmaceuticals, Piscataway, NJ; DepoCyt®, Mundipharma, Cambridge, UK), a sustained-release formulation of cytarabine encapsulated into multivesicular lipid-based particles, was developed to address these issues. This liposomal formulation has a half-life of 100 to 263 hours after intrathecal or intraventricular administration at a dose ranging from 12.5 mg to 75 mg, compared with only 3.4 hours after intrathecal administration of 30 mg of free (non-liposomal) cytarabine. Hence, while...
a single injection of free cytarabine results in cytotoxic concentrations (≥ 0.1 µg/mL) in the CSF for less than 24 hours, a single administration of liposomal cytarabine maintains therapeutic CSF levels for at least 8 days in children. Liposomal cytarabine administered at a dose of 35 mg every 2 weeks was effective in the treatment of refractory CNS leukemia in children (Bomgaars et al., 2004). However, liposomal cytarabine should not be given before or during treatment with high-dose chemotherapy that penetrates the blood-brain barrier because this treatment schedule can result in clinically significant neurotoxicity (Jabbour et al., 2007).

Regardless of the type of intrathecal treatment used, careful attention should be paid to its optimal administration. For example, intrathecal medication given in a large volume (6 ml or more) should attain a better distribution within the CNS than in a smaller volume. After the procedure, patients should remain in the prone position for at least 60 minutes, which in a nonhuman primate model was shown to increase significantly the intraventricular level of medication (Pui & Howard, 2008). Traumatic lumbar puncture should be avoided, especially at diagnosis when the majority of patients have abundant circulating leukemic blasts. Thrombocytopenia and coagulopathy should be corrected before the diagnostic lumbar puncture which should be followed immediately by intrathecal treatment to avoid the need for repeated procedure within the first few days. The diagnostic procedure should be performed by the most experienced clinician and preferably with patients under deep sedation or general anesthesia.

**Systemic chemotherapy**

Systemic chemotherapy such as high-dose methotrexate, dexamethasone, thioguanine and thiotaepa, can influence the control of CNS leukemia in ALL (Pui & Evans, 2006). In general, patients treated with dexamethasone had lower rates of CNS relapse and better event-free survival rates than those treated with prednisone (Pui & Howard, 2008). Thioguanine is more potent than mercaptopurine in model systems and results in higher concentrations of thioguanine nucleotides (active metabolites) in cells, as well as cytotoxic concentrations in CSF. Thioguanine, given at a daily dose of 40 mg/m² or more, produced superior antileukemic responses and significantly lower CNS relapse rates, as compared with a conventional dose of mercaptopurine (75 mg/m²), but was associated with profound thrombocytopenia, an increased risk of death in remission, and an unacceptably high rate (10% to 20%) of hepatic veno-occlusive disease (Stork et al., 2002; Vora et al., 2006). While mercaptopurine remains the drug of choice for ALL, it remains to be seen whether short courses of thioguanine could improve outcome without adding undue toxicity. Of interest, thiotaepa administered intravenously at 65 mg/m² as a single agent to 9 patients with B-cell precursor ALL and isolated CNS relapse resulted in three complete and four partial remissions with an overall response rate of 78% (Barredo et al., 2006).

Little is known about the effect of systemic chemotherapy on CNS control in AML. In general, high-dose cytarabine and cladribine are considered to contribute to CNS control because they are known to penetrate the CNS better than other agents used for the treatment of this disease.

**Treatment of CNS Relapse**

The strategy of delaying cranial or craniospinal irradiation for 6 to 12 months to allow initial intensification of systemic chemotherapy has improved long-term second event-free survival rates to 70% to 80% and reduced the rate of neurotoxicity in children with an isolated CNS relapse of ALL (Pui & Howard, 2008). In a Children’s Oncology Group which tested the reduction of radiation dose, patients with an initial remission duration < 18 months received 24 Gy cranial and 15 Gy spinal irradiation, and those with a longer initial remission received only 18 Gy cranial irradiation at 12 months of treatment. Despite the reduction of radiation dose, patients whose initial remission persisted for more than 18 months had an excellent 4-year event-free survival rate of 77.7% (Barredo et al., 2006). It should be noted that this result applies only to children with B-cell precursor ALL who did not receive cranial irradiation during initial treatment. Interestingly, besides a long initial remission, a standard-risk status at diagnosis by NCI/Rome criteria (i.e., age 1 to 9.9 years with leukocyte count < 50 x 10⁹/L) was an independent favorable prognostic factor in the study. It is also noteworthy that isolated or
combined CNS relapse accounted for 8 of the 11 subsequent relapses in this study and for 26 of 44 subsequent events in another study (Tsurusawa et al., 2007), suggesting the need for further improvement in CNS control. A recent study showed that submicroscopic involvement of bone marrow was a frequent finding in patients with "isolated" CNS relapse, and was associated with a very poor prognosis (Hagedorn et al., 2007). Some investigators advocate the use of allogeneic or autologous transplantation for CNS relapse in patients with a short initial remission duration, T-cell ALL, prior cranial irradiation, or the presence of submicroscopic bone marrow disease, because these patients have a poor prognosis with chemotherapy. However, there are no conclusive clinical trials to support this approach. In one recent study, 8-year leukemia-free survival adjusting for age and duration of first remission was comparable between 149 patients treated in two chemotherapy trials and 60 patients transplanted with HLA-matched sibling donors (Eapen et al., 2008). It should be noted that this is not a randomized study, and conceivably there was selection bias. Even less is known about the optimal treatment for patients with isolated CNS relapse of AML.

Future Directions

Despite impressive gains in the management of CNS disease in children with leukemia, more effective treatment is clearly needed for patients who have had a CNS relapse or have a very high risk of developing this complication. Treatment strategies that could improve outcome in these subgroups include frequent and early intrathecal therapy as used for Burkitt leukemia/lymphoma, intrathecal liposomal cytarabine, and intraventricular administration of chemotherapy. Ongoing studies are testing whether the dose of cranial irradiation can be further reduced in ALL patients with isolated CNS relapse and long initial remissions. In AML, the relative efficacy of triple intrathecal therapy versus cytarabine alone remain to be determined.

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Paediatric Oncology - The Past and the Future

A.W. Craft

2008 marks the 40th anniversary of the founding of the Societe Internationale Oncologie Pediatrique or SIOP as it has become widely known. The highlight of the year's activities has always been the annual scientific meeting and this year it is being held in a most appropriate situation - Berlin. This city is famous for many things and amongst the illustrious alumni is Rudolf Virchow the polymath who is credited with one of the first descriptions of leukaemia. He was a man of many parts but pathology was his prime interest and he is perhaps best known for his theory

Omnis cellula e cellula - Every cell originates from another cell like it

This phrase was actually first used by Raspail but there is no doubt that Virchow popularised it. Prior to this it was thought that life could arise spontaneously eg maggots could spontaneously generate in rotting meat.

Virchow worked in the Charite Hospital, Berlin, which now houses a museum in his honour

SIOP emerged in the late 1960s building on a series of training courses and informal meetings which had largely been inspired by Odile Schweisguth from Paris.

A society was formed with members from both Europe and the United States. Their aim was to work together to try and improve the care of children with cancer and to do this by collaboration in clinical trials and coming together at an annual scientific meeting.

In 1970 the survival for childhood cancer was poor with at best 40% of children able to be cured with either surgery or the addition of radiotherapy. The place of chemotherapy was just beginning to be explored and it was the excitement around the possibilities for this new modality which drove the formation of the new International Society.

There had always been a small number of patients who could be cured by surgery alone. Osteosarcoma for example has always had a 20% survival rate for amputation alone and other localised diseases eg soft tissue sarcomas and Hodgkin's disease could be treated with excision. The advent of radiotherapy in the early part of the last century led to some improvements in survival particularly for those localised tumours which could not be completely resected.

The serendipitous discovery of cytotoxic chemotherapy in the 1940s led to the development of a new generation of drugs which provided real hope for those cancers which were clearly disseminated and not amenable to localised therapy.

Acute lymphoblastic leukaemia was one of the first diseases to benefit from this new form of therapy. One of the pioneers in this field was the St Jude Children's Research Hospital in Memphis where in a series of "Total" studies steady improvements in survival were seen. Another important breakthrough came when there was recognition that although survival was prolonged the pattern of relapse changed and for many death still ensued. The concept was evolved that there might be sanctuary sites of disease that were not so readily amenable to the oral or systemically administered chemotherapy. This led to CNS directed therapy, initially in the form of cranial or craniospinal irradiation and intrathecal chemotherapy.

In solid tumours too chemotherapy became an important adjunct to surgery and this was well shown in Wilms' tumour which was found to be very chemoresponsive. Wilms' of course was another eminent German who has lent his name to paediatric oncology.

Progress in both leukaemia and solid tumours has been facilitated by the formation of cooperative groups set up to carry out clinical
trials. Initially survival prospects were so poor that it was possible to carry out either large single Institutional studies or national studies. However as survival has improved the incremental gains from new treatments has become proportionately smaller and it has been necessary to move to international studies which can accrue sufficient patients in a timely manner to answer relevant questions. SIOP has played an important part in this international effort to find better treatments.

The philosophy of treatment has changed over the past 40 years. When survival prospects were very poor it was justifiable to have a concept of "cure at any cost". However improved survival brought with it a recognition that there were significant "late effects" of treatment. This was clearly evident in ALL where neuropsychological impairments were seen following CNS directed therapy as well as the late effects of radiotherapy and of the anthracycline group of drugs which cause cardiotoxicity.

The philosophy of treatment therefore changed to one of "cure at least cost". This was aided by the recognition that prognostic factors could be identified in some tumours at the time of diagnosis which allowed treatment to be stratified into good and poor prognosis. Treatment could then be intensified for the poor prognosis and reduced for the better prognosis groups.

Many of the initially identified prognostic factors were clinical or based on simple measurements such as total white blood cell count in leukaemia. However a better understanding of the biology of childhood cancer, including cytogenetics, has allowed an increasingly sophisticated ability to predict outcome.

Modern studies therefore almost inevitably include a concurrent biological study and increasingly tissue is stored to facilitate future research.

Supportive care has been recognised as an important core part of the care of children with cancer. In the early days of chemotherapy it was not unusual for a child to die from overwhelming infection. These were usually bacterial but with the improvements in antibacterial therapy fungal infections emerged as important pathogens. Now febrile neutropaenia remains a common part of the life of a child being treated for cancer but most infections are relatively minor and in some centres these are now treated with home antibiotics. However vigilance remains important and except for the very poor prognosis patients doses of chemotherapy are adjusted to try and minimise the occurrence of secondary infection.

One of the stated aims of SIOP is to ensure that the benefits of modern therapy are brought to the widest group of children worldwide. The Paediatric Oncology in the Developing Countries (PODC) group was established some 20 years ago to begin this process and over the last 2 decades we have seen increasing numbers of children being successfully treated from all over the world. One of the real challenges however is to find economically viable treatments. The relatively simple treatments developed many years ago are often reasonably effective and can cure children at much less financial cost. The extra cost of more complicated treatments is often exponential for very little health gain. The question of supportive care is also important for developing countries and the availability of broad spectrum antibiotics can be a rate limiting step in the successful treatment of the cancer.

SIOP has played its part in this drive to offer some hope to the vast majority of the world's children who currently develop cancer and have access to either no treatment or very limited treatment. It has been estimated that over 80% of the children in the world who get cancer are in this category.

New and simple treatments for Burkitt's lymphoma in Africa have been pioneered by both SIOP and the French group working in francophone Africa.

In India Agarwal and his colleagues, with the help of SIOP and WHO pursued the important line of trying to capacity build. They established a system of training the trainers in cost effective treatments including supportive care. This has now been rolled out across the Indian subcontinent and is beginning to make a real difference to the huge numbers of children who develop cancer each year.

Many centres in the developing world have linked with others in more well off countries and there are many examples of these. The links
between Monza in Italy and Nicaragua, Berlin and Moscow, and the French connections with Africa are good examples. More recently this form of education and encouragement has been facilitated by the outreach programmes of the St Jude Hospital in Memphis. The internet has been a very powerful tool along with videoconferencing to bring new ideas and expertise to all parts of the globe.

A major landmark was reached in Mumbai when they were able to set up a late effects clinic. Only 10 years previously it had been said that they would “jump for joy” if they reached this landmark. This is an important milestone in the development of paediatric oncology in any country.

For those of who work in the more economically advantaged countries it comes as a surprise to see reports of studies in emerging countries when one of the largest categories of patients at follow up are described as “abandoned treatment”. There are many reasons why patients and their parents might abandon potentially curative treatment and cost of drugs is but one. The need for parents to return to work and the acceptance that a prolonged treatment is actually needed are others. Education of populations in health matters and of the importance of prolonged periods of treatment is essential.

Although survival rates have increased dramatically over the last 40 years there are still about one third of children who go on to die of their cancer and this is higher in parts of the world where treatment possibilities are not so readily available. Symptom management and palliative care have been areas which have seen important developments over the last 2 decades and nurses have been at the forefront of this very important field. The place of death is an important measure of the quality and depth of services in well developed countries. Most parents, and children where they are able to give an opinion, would prefer to die at home in their own bed surrounded by their family, friends and belongings. In order for this to happen there needs to be investment and training in paediatric oncology outreach nurses. This an expensive service but when compared with hospital admission it can be economically viable. Palliative care for children with cancer has led the way to the development of palliative care as a specialty for all children who have life threatening or life limiting disease.

Much effort has been expended in the field of adult cancer into early detection and prevention. Unfortunately such efforts have not been fruitful in children.

Neuroblastoma appeared to be an ideal candidate tumour for screening when it became clear that diagnosis at an early age, less than 1, and early stage, was clearly associated with improved survival. There was also an easily measurable urinary marker in 95% of cases in the form of catecholamine metabolites. Pioneering studies in Japan looked very promising but increasingly there was a recognition that screening programmes were substantially increasing the incidence of the disease. This was due to the detection of many early stage tumours which would otherwise have spontaneously regressed. Two major randomised trials in Canada and in Germany failed to show any benefit for screening and it has been abandoned in most parts of the world. However all of the efforts around screening helped to clarify that neuroblastoma is probably at least 2 diseases and that these are correlated with clear biological characteristics of the tumour. Good prognosis tumours have low levels of nMyc and the converse for poor prognosis. Treatment is now stratified dependent on biological factors determined at the time of diagnosis. There is still a small part for screening in childhood cancer but this is only suitable for identifiable groups of high risk patients where early diagnosis can be shown to be of some benefit and there is a simple screening test. There are some groups at high risk of developing Wilms’ tumour eg those with aniridia of Beckwith-Wiedeman syndrome and regular abdominal ultrasound examinations are now recommended.

There are some interesting recent data to suggest that the pattern of general health surveillance for children can influence outcome for children with Wilms’ tumour. Survival for Wilms in Germany is about 9% higher in Germany than the UK. Much of this difference can probably be ascribed to the earlier detection of the tumour in Germany. 25% of Wilms’ tumours are picked up in Germany at a routine health check in the first year of life or as an incidental finding at a medical encounter for
some other reason. For the UK it is around 10%. The patients picked up in this way have a better outcome. In Germany there are many more routine health examinations and these are done by a trained primary care paediatrician who is likely to have an ultrasound machine in his office, and to know how to use it. In the UK children are seen by general practitioners on a very limited number of occasions. The German system is much more expensive and cannot be justified economically on the basis of early detection of Wilms. However the UK will need to look at the way it carries out health checks in children.

Prevention is an even more despairing story for children. Prevention depends primarily on an understanding of what causes childhood cancer. Apart from abdominal irradiation from x-rays in the early stages of pregnancy causing an increased risk of leukaemia and the administration of diethylstilboestrol to mothers causing vaginal cancer in their offspring there are few concrete examples to help. There is increasing evidence to suggest that much of childhood cancer has its origins in utero. There have been exciting studies in leukaemia where genetic mutations have been found in the dried blood spots taken at birth of children who subsequently develop leukaemia. A major recent paper in Science studied twins, both of whom had genetic changes on their bloodspots but only one developed leukaemia suggesting that a prenatal* hit* may be a high risk factor but some sort of postnatal event must also occur.

So, in 2008 we are at a point where with optimum treatment the survival prospects for children with cancer are at least 75% and for some groups eg good risk leukaemia and Wilms' tumour survival chances are well into the 90% range.

**Where do we go next?**

We will continue to refine the treatments that we already have available. Increasingly it will be possible to look at individual pharmacogenetics and personalise treatment to an individual's phenotype and genotype. However this will be very expensive given the relative rarity of cancer in children. It is a principle which is much more likely to be applicable to high volume adult tumours.

We must continue to search for the "magic bullets" which will be drugs, or perhaps even other modalities, which target the tumour and spare normal tissues. Increasingly drug discovery programmes will identify specific targets in a tumour and the medicinal chemists will produce a drug designed to interact with that target. Ewings tumour would seem to be an ideal candidate for this approach as there is a very specific chromosomal translocation and gene product associated with it. So far a specific drug has eluded discovery but there are several promising lines of research currently being pursued.

New modalities of therapy are also needed. It has long been known that dogs can be cured of osteosarcoma by BCG. The recent randomised trial of a form of immunotherapy in the form of muramyl tripeptide in children with osteosarcoma showed a clear benefit of this new therapy and further studies are now being planned. New ideas are badly needed in osteosarcoma where treatments and outcome have changed little in 25 years.

International collaboration is now paramount if we are going to make rapid progress and bring possible exciting new therapies to all patients as soon as practically possible. However there are barriers to progress, not least of which is the growing bureaucracy around clinical trials. Legislators have put in place sophisticated systems to protect patients but unfortunately these run the risk of actually harming patients by denying them access to well tried and tested new drugs. We have come a long way in 40 years and Virchow would not believe what we are now able to do.

Hopefully the next 40 years will see a progressive understanding of what childhood cancer really is. This better understanding should lead to better treatments and perhaps also to prevention. There are real hopes for new and more specific drugs but these are hugely expensive to develop and the pharmaceutical industry will need real incentives to develop drugs which will only be used in children. There are now such incentives in place both in the US and Europe but they still rely on the drug being potentially useful for the high volume adult market.

Childhood cancer is curable and we must ensure universal access to cost effective therapies.
Protons for Childhood Brain Tumors: Current Experience and Future Promise

Nancy J. Tarbell, Shannon M MacDonald, Torunn I Yock,

Introduction

The primary aim of any cancer therapy is to eliminate malignancy and render a patient cancer-free. Fortunately, advances in the treatment of pediatric brain tumors over the past few decades allow many children to enjoy life free of their malignancies. Sadly, though, with improved long-term survival comes a better understanding of the substantial detrimental impact that cancer therapies can have on quality of life. Late toxicities of treatment are particularly apparent in children that have received radiation to the brain and central nervous system (CNS). The realization of the impact of late toxicities has led to increased efforts to maintain tumor control while decreasing adverse consequences of treatment.

Radiation has been proven an effective modality for the control of pediatric brain tumors. Unfortunately, it is a cure that can lead to significant sequelae that can impact daily life and even prevent normal functioning in society. Well documented side effects from CNS radiation include neurocognitive, neuroendocrine, and auditory dysfunction as well as second malignancy. Craniospinal irradiation (CSI) carries additional risks of cardiac and pulmonary dysfunction, hypothyroidism, gastrointestinal effects, growth abnormality, and infertility. Investigators have attempted to avoid radiation therapy in order to spare late effects, especially for the very young. Although many studies have documented responses to chemotherapy, these trials have also reported high rates of local recurrence. More successful efforts have aimed to reduce the volume of irradiated tissue, often in combination with chemotherapy. Technical advances in imaging and radiation therapy aim to define and treat the appropriate area while simultaneously sparing uninvolved healthy tissues. Proton therapy represents an effective, albeit expensive, way to avoid unwanted dose to the surrounding normal tissues. It is currently available in only a handful of select centers around the world. However, knowledge of many of the physical advantages of proton therapy has spread rapidly over the past several years and many facilities are currently in planning or construction phases. Given the higher costs of proton therapy, it is our obligation to determine which patients stand to derive substantial clinical benefit from proton radiation as compared to photon radiation. Recognizing the sensitivity of developing tissues, high risk for development of a second malignancy, and the considerable cost to society of caring for chronic medical problems and the developmentally delayed, curable pediatric CNS tumors represent one of the clear indications for proton radiation.

Proton Radiation: Comparison to Photon Radiation

The benefit of protons versus photons is derived from the physical properties of the proton particle itself. Protons are charged particles that enter tissue delivering a small and relatively constant dose until near the end of the proton range where the majority of dose is delivered to the same side of the path. This distal portion of the proton beam is defined as the Bragg peak and no dose is delivered to tissues distal to the Bragg peak. Protons have a defined range or depth in tissue that is directly proportional to the energy of the beam itself. The cyclotron at the Francis H. Burr proton center is capable of producing a beam with a maximum energy of 234 MeV with a range of 32 cm in water, allowing for the treatment of deep seated as well as superficial tumors.
dose to a target greater than one cm in the path of the beam, multiple Bragg peaks of different energies are stacked to form what is referred to as a Spread Out Bragg Peak (SOBP). This increases the entrance or skin dose, but still allows full sparing of all tissues distal to the tumor volume and dose proximal to the target is still generally lower than dose delivered with photons. In contrast, photons deliver dose both proximal and distal to the target. Photon depth or range is also proportional to energy, but the depth at which the maximal dose is delivered is limited to a range of approximately 3-4 cm. To treat to a greater depth the dose proximal to the tumor volume must be greater, and for this reason treatment is generally delivered with multiple fields; to avoid excessive dose multiple fields are used. Intensity modulated radiation therapy (IMRT) is the most advanced form of photon radiation currently available. IMRT accomplishes excellent conformity to target volumes while decreasing high dose to specified avoidance structures. This is accomplished by a sophisticated computer planning system and delivery of radiation through multiple small fields and beam angles. One of the major disadvantages of IMRT is the increase in low dose to a larger amount of normal tissue.

Proton radiation is prescribed in Cobalt Gray Equivalents (CGE) as opposed to Gray (Gy), which is used for prescribing photon radiation. This takes into account the slightly higher Relative Biological Effectiveness (RBE) of proton beams. Relative Biological Effectiveness is defined as the dose required to achieve a biological effect with photons compared to the dose required for a certain test radiation, in this case, protons. Experimental studies have determined an average RBE of 1.1 for proton therapies. This value has been widely accepted among clinical proton facilities and is used to calculate CGE. Thus, prescribed dose and biological effects of protons should be biologically equivalent to photon radiation. Therefore, the advantage of protons in how it is employed is a physical advantage; not a biological advantage.

Clinical Experience for Childhood Brain Tumors

Medulloblastoma

Medulloblastoma is an embryonic neoplasm arising from the cerebellum. It accounts for approximately 20% of pediatric brain tumors and is the second most common pediatric brain tumor following pilocytic astrocytoma. Median age of onset is 5-6 years of age. For patients with standard risk disease, cure rates exceed 80%. Long-term survival is less for patients with high-risk medulloblastoma, but 5 yr disease free survival rates of 60-70% can be achieved. The excellent survival for this group of patients underscores the importance of decreasing late toxicity. Standard radiation therapy for medulloblastoma consists of treatment to the entire craniospinal axis to a dose of 23.4 Gy/CGE to 36 Gy/CGE followed by a boost to the involved region or posterior fossa to bring the total dose to this region to 54 Gy/CGE. St. Clair et al published a comparison of dose distributions for craniospinal radiation followed by a posterior fossa boost for standard photons, IMRT, and protons. Figure 1

**Fig 1:** Depicts proton craniospinal radiation (CSI) prescribed to a dose of 23.4 CGE for a child with medulloblastoma. Sagittal image demonstrates sparing of organs anterior to the vertebral bodies. Axial image at the level of the cribriform plate demonstrate conformal treatment to this region.
demonstrates sparing of organs anterior to the vertebral bodies for proton therapy. This study demonstrated dose received by 50% of the heart to be 72% for photons, 30% for IMRT, and < 1% for protons. Although IMRT decreased dose to the heart compared to standard photons, IMRT increased dose to other vital organs including lung and kidneys. Dose to 90% of the cochlea was also substantially decreased with protons. For standard photons, the cochlea received full prescription dose (101%). With IMRT this was reduced to 33%, and with protons it was decreased to 2%. Standard chemotherapy for medulloblastoma includes cisplatin, which can also cause hearing loss making it even more important to spare the cochlea from radiation. Proton radiation also decreases dose to the supratentorial brain and neuroendocrine structures. Currently, an ongoing study at the Massachusetts General Hospital is collecting data on acute and long term outcomes for the use of proton radiation for patients with medulloblastoma.

**Germ Cell Tumors**

Germ cell tumors of the central nervous system are relatively rare accounting for less than 4% of pediatric brain tumors. These tumors typically arise within the suprasellar region or pineal gland, but may occur elsewhere in the brain. They are often localized, but dissemination to the craniospinal axis is not uncommon. Pure germ cell tumors promptly respond to treatment with radiation and durable cures are obtained in approximately ninety percent of patients at 10 years with radiation alone. Recent clinical trials have used smaller RT volumes and reduced dose in patients with localized disease experiencing a complete response to neoadjuvant chemotherapy. Patients with disseminated disease at diagnosis are still treated with craniospinal RT but at a lower dose. The experimental arm of the new phase III Children's Oncology Group study (ACNS0232) for CNS germinoma attempts to reduce RT volume and dose in patients with localized disease to involved field rather than whole ventricular if a complete response is observed following neoadjuvant chemotherapy. Figure 2 depicts proton radiation treatment to the ventricles. For patients with non-germanomatous germ cell tumors, outcomes are not as favorable and standard radiation therapy includes craniospinal radiation. For patients receiving craniospinal RT, similar benefits in sparing of structures anterior to the vertebral bodies through the use of proton radiation is seen. Involved field radiation to the initial site of disease for those patients receiving neoadjuvant chemotherapy on trial can spare uninvolved brain and critical structures in the proximity of tumor volumes.

**Ependymoma**

Ependymomas are relatively rare malignancies accounting for 8-10% of intracranial pediatric tumors, with most cases occurring in children under the age of four. One-third of intracranial childhood ependymomas occur in...
the cerebral hemispheres. The remaining two-thirds occur in the posterior fossa. Standard treatment for both supratentorial and infratentorial ependymoma consists of maximal surgical resection followed by radiation therapy. Control rates near 80% have been achieved with for localized ependymoma using involved field radiation and this has evolved as the standard of care. The young age and excellent outcomes that can be achieved with surgery and radiation make protons an attractive radiation modality for patients with localized ependymoma. The Massachusetts General Hospital recently reported early outcomes for patients with localized ependymoma treated with involved field proton radiation. At a median follow-up of 26 months from the start date of radiation therapy, local control, progression-free, and overall survival was 86%, 80%, and 89%, respectively. This study also performed dosimetric comparisons for both infratentorial and supratentorial ependymomas for IMRT, protons, and intensity modulated proton therapy (IMPT). IMPT is a more sophisticated form of proton therapy with very limited clinical availability at this time. It is likely that IMPT will become widely available at proton centers over the next decade. In this study, comparable tumor volume coverage was achieved with IMPT, proton therapy, and IMRT. Substantial normal tissue sparing of structures including brainstem, cochlea, pituitary gland, hypothalamus, temporal lobes, and whole brain was seen with the proton therapy plan as compared to IMRT. The use of IMPT will allow for additional sparing of some critical structures while using a decreased number of beam angles. Figure 3 demonstrates dose distributions for IMRT, protons, and IMPT for a patient with an infratentorial ependymoma.

**Astrocytomas/Optic Pathway Tumors**

Astrocytomas are the most common pediatric CNS tumor, with low grade astrocytoma being the most common subtype. Low grade astrocytomas can be cured by surgery alone when they occur in locations amenable to gross total resection. When these tumors arise in locations that are inoperable they are often treated with chemotherapy to avoid or delay radiation. Approximately 20 to 30% of low grade astrocytomas occur in one or multiple components of the optic pathway. Optic pathway gliomas occur most commonly in the first decade of life and about 1/3 of patients with these tumors carry the diagnosis of neurofibromatosis type I (NF1). NFI patients with optic gliomas have a better prognosis, but are also at increased risk of second malignancy and are at increased risk of learning disabilities as a result of NF1. Optic pathway gliomas are not surgically resectable and if they do not regress spontaneously or respond to chemotherapy, patients may experience visual loss. Radiation therapy is recommended for patients with unresectable low-grade astrocytomas that do not respond to chemotherapy. When radiation is required, local radiation to a dose of approximately 50.4-54 Gy is recommended. Although normal CNS structures spared are dependent on tumor location, protons can provide increased normal tissue sparing that is critical for these young children with highly curable disease, particularly in the context of proton therapy for localized ependymoma.

**Fig 3:** Demonstrates IMRT, Proton, and IMPT plans for a young girl with a localized ependymoma. Axial CT slices at the level of the pituitary demonstrate sparing of the pituitary, temporal lobes, and brainstem with the use of proton therapy and IMPT.
in the setting of NF1. Figure 4 shows a proton plan for a large optic pathway tumor. Loma Linda University reported outcomes for 7 children treated with protons for optic pathway tumors and compared proton plans to 3D conformal photons and opposed lateral photon fields. At a median follow up of 37 months, all patients were alive without disease progression. Proton radiation decreased dose to the uninvolved optic nerve, temporal lobes, optic chiasm, and pituitary gland compared to both photon plans. Hug et al also reported outcomes for low grade gliomas including optic pathway gliomas and low grade brainstem glioma. They reported 3 year follow up for the first 27 patients treated at Loma Linda University and demonstrated favorable local control, survival, and toxicity at this time point. Anaplastic Astrocytoma and Glioblastoma Multiforme are less common in the pediatric population and with current available treatments these tumors are not considered curable. It is not clear that these patients with more aggressive tumors will derive substantial benefit from proton radiation as compared to photon radiation.

**Craniopharyngioma**

Craniopharyngiomas are histologically benign tumors that arise from remnants of Rathke's pouch that often contain both solid and cystic components. They often involve or are in close proximity to vital structures in the sellar region including the pituitary and optic chiasm. The location makes a gross total resection difficult and often impossible without significant surgical morbidity. When resection is incomplete, approximately 70% of these tumors will show progression within a few years. Limited surgery followed by radiation achieves excellent control. The target volume includes the postoperative bed and residual disease with a tight margin. A dose of approximately 52.2 to 54 Gy/CGE is recommended. Proton radiation can provide substantially decreased dose to the surrounding temporal lobes and brain. Fitzek et al reported outcomes for 15 patients with craniopharyngiomas treated with mixed modality photon/proton radiation for craniopharyngiomas. Local control at 5 and 10 years were 93% and 85 %, respectively. The current policy at the Massachusetts General Hospital is to treat patients with craniopharyngiomas to deliver the full radiation dose with protons.

**Second Malignancy**

When delivering radiation therapy to the adult population, minimizing the dose to organs that are already below the normal tissue tolerance may not provide a large clinical benefit. However, for children who will survive for many years after therapy, the probability of late complications or radiation-induced malignancies is much greater. Miralbell et al. assessed the potential influence of improved dose distribution with proton beam radiation and IMPT as compared to 3D conformal photon radiation and intensity-modulated photon beam radiation (IMRT) on the induction of second malignancies.

![Fig 4](image-url): Shows a treatment of a very large optic glioma with proton radiation. Axial, sagittal, and coronal images demonstrate sparing of normal brain tissue with highly conformal proton radiation.
of second malignancy was estimated with a model based on guidelines from the International Commission on Radiologic Protection. IMPT was superior to other modalities with regard to reduction in second malignancy risk. The expected risk of radiation-induced malignancy for IMPT was almost 2.4 times lower than the conformal photon plan and about half the risk expected for IMRT. Standard protons and IMPT decreased the estimated risk as compared to photon planning with or without intensity modulation.

**Future Research and Conclusions**

Proton radiation for childhood brain tumors is an excellent application for this advance in technology. Dosimetric comparisons show excellent conformity to target volumes with superior sparing of surrounding healthy tissues. Early outcomes are surfacing in the literature and publications reporting late toxicities should become available over the next several years.

At this time, most proton therapy is delivered through passive beam-scattering methods with use of patient-specific hardware such as range compensators and apertures. Scattering foils and range modulators are responsible for the size and homogeneity of the SOBP. Range compensators and apertures are custom designed to deliver a homogeneous dose distribution (SOBP) to the target with optimal dose conformity at the distal target region for each field. Although some intensity modulation is inherent in these proton plans, they are still not considered to be IMPT plans. Similar to IMRT, IMPT refers to plans that deliver a homogenous dose to the target with the superimposition of individually inhomogeneous fields. In other words, IMPT fields are generated by thousands of individual pencil-sized beams (Bragg peaks) modulated in energy and intensity, and optimized with an inverse planning system. Although this greatly increases the complexity of the plan, it allows for increased dose-shaping capabilities with optimal conformity not only at the distal region of the target but also to the proximal target edge. IMPT cannot be efficiently delivered with passive scattering beams alone and requires the implementation of active scanning methods.

At the present time, IMPT is applied routinely in only one center, The Paul Scherer Institute in Switzerland, using the spot-scanning technique.

The price of proton radiation is substantially greater than photon therapy and although the difference may diminish with time, proton therapy will, in all likelihood, remain more expensive. Long-term cost-benefit analyses will need to be performed in an attempt to determine if proton therapy is truly "cost effective" for pediatric patients with CNS tumors. Quality of life models are not without fault due to the inability to place an accurate value on sparing any future morbidity for a young child unfortunate enough to face the burden of a malignancy. Alas, they are our current best estimate of the value of a very costly treatment and are worth in preventing future costs to society. In our opinion, pediatric CNS malignancies represent one of the most worthy indications for proton radiotherapy because it better spares normal tissues over any external beam photon technique.

**References**


Liver tumours and The SIOPEL story

Daniel C. Aronson

Historical background

One hundred and ten years ago, the first case report of a hepatoblastoma (HB) was published in the English literature in 1898 by Misick in Prague. Under the title 'A case of Teratoma Hepatis', a 6-week old boy was described who died of respiratory problems. Autopsy showed a large tumor that occupied the lower half of the right liver lobe. Cysts, cartilaginous and bony deposits were seen, as well as venous tumor infiltration. It was therefore not surprising that the tumor was described as a teratoma, with tissue representatives of the three embryonic germ-cell layers. More than sixty years later in 1962, Willis introduced the term 'Hepatoblastoma' for this type of tumor that he defined as 'an embryonic tumor that contains hepatic epithelial parenchyma'. At that time, usually hepatoblastoma was not distinguished from hepatocellular carcinoma (HCC). Through the work of Ishak and Glunz in 1967, morphologic criteria were defined for HB and HCC that were refined in the decennia that followed.

Epidemiology

Incidence

Hepatoblastoma is a malignancy of the liver with a fairly constant annual incidence of 0.5-1.5 cases per million children younger than 15 years of age in Western countries, with a small increase reported in the USA. It comprises 1% of all pediatric malignancies and affects mostly infants and young children between 6 months and 3 years, but cases in neonates and adolescents have also been reported. After neuroblastoma and nephroblastoma, primary epithelial tumors of the liver are the third most common intra-abdominal neoplasms in children. Hepatoblastoma is the most frequent liver tumor in Western countries. In Asia and Africa, hepatocellular carcinoma (HCC) occurs more frequently than HB, which is probably a consequence of the higher prevalence of hepatitis B infection on those continents.

Risk factors

Thus far, no environmental risk factors for HB have been described, but HB has been associated with prematurity or a low birth weight. Familial cases have been reported. In this respect, the coincidence of HB with familial adenomatous polyposis (FAP) and Beckwith-Wiedemann syndrome (BWS) is striking and suggests a role in the pathogenesis of HB for chromosomes 5 and 11, respectively.

The baseline: a survey

In 1975, Exelby published the landmark paper that has been cited in most of the papers dealing with liver tumors in children, in which he reported the American Academy of Pediatrics Surgical Section Survey - 1974.

Through questionnaires sent to the members of the Surgical Section of the Academy of Pediatrics, data on liver tumors in children operated upon during the previous 10 years were requested. From 110 replies, 375 liver tumors were reported of which 252 were malignant (hepatoblastoma [n=129] and hepatocellular carcinoma [n=98]) and 123 benign. In 15% of the HB patients the tumor was multicentric in origin. In HCC both lobes were involved in almost 45% of the patients, and in 30% the tumor was multicentric. All patients with hepatoblastoma underwent primary surgical exploration. A definitive procedure was carried out in 86 patients and biopsy only was carried out in 43. Seventy-eight patients had complete excision of the tumor for cure and 45 (60%) survived. In two-thirds of the patients, the tumor was not excised completely and there were no
survivors in this group. The over-all survival rate in hepatoblastoma was 35% and in hepatocellular carcinoma 13%.

Excessive blood loss was the most common complication during and immediately after operation, after which cardiac arrest occurred in nine patients. There were eight deaths in the operating room and 17 deaths in the immediate postoperative period attributable to the operation.

In the hepatoblastoma patients irradiation was given to the liver in 15, chemotherapy utilizing a wide variety of agents was used in 53 patients. It was apparent that no cures were obtained from irradiation and/or chemotherapy in inoperable cases. There were three cases of hepatoblastoma, however, in which the patients who were originally thought to have inoperable tumor and became operable after irradiation to the liver and combined chemotherapy of vincristine, actinomycin, and cyclophosphamide. These three patients were long-term survivors after subsequent hepatic lobectomy. In the patients with hepatocellular carcinoma, there was no proven effect of irradiation or chemotherapy. Eleven patients were given prophylactic chemotherapy after complete surgical excision of the tumor and eight of these patients were alive.

When incomplete excision or biopsy only was carried out no patient survived in either group. There was no evidence that radiation therapy or chemotherapy controlled disease which could not be completely excised surgically. At this time it seemed that complete operative excision offered the only chance of cure in children with these tumors through which cure rates in this subgroup of patients of 60% could be achieved in hepatoblastoma and 33% in hepatocellular carcinoma.

Management

As has become clear nowadays, surgery alone can cure very few patients. More than half of the patients present with unresectable primary tumours or distant metastases. In the early series of patients treated with surgery alone, there was a 30% relapse rate in those patients whose tumour could be completely resected. Evidence that HB is a chemosensitive tumour began to accumulate in the early 1970s when responses were seen to combinations of cyclophosphamide, vincristine, 5-fluorouracil and actinomycin-D, but not until the introduction of cisplatin- and doxorubicin-containing regimens in the 1980s was there a major impact on survival. Twenty years later, cisplatin still remains the backbone of the chemotherapy regimen. Chemotherapy may reduce tumour volume making the tumour resectable and may lead to the complete disappearance of lung metastases. The tumour response rate to the present cisplatin-containing chemotherapy regimens varies from 70 to 90% according to the different series. Neo-adjuvant chemotherapy not only makes the tumour 'smaller' and consequently more likely to be completely resected, but also more solid, less prone to bleeding and more demarcated from the remaining healthy liver parenchyma. Also (micro)metastases in the lung have no delay in treatment. Because of all these reasons some study groups currently recommend to start treatment, after biopsy, with preoperative chemotherapy, deferring definitive surgery until after 2 to 3 months of therapy. This is the treatment philosophy as adopted by the SIOP Liver Tumour Study Group (SIOPEL). In contrast to the SIOPEL approach, the North American Study Groups (first CCSG and POG, now COG) still recommend primary surgery, whenever prudently possible, as the initial treatment. So far, no controlled comparison has been done between the two therapeutic strategies, primary chemotherapy versus primary surgery, in terms of overall survival rates. However, the present survival rates of the different study groups are comparable, projecting 3-year overall survival rates, regardless of the first therapeutic modality used, of 62 to 70%.

Staging

A universally accepted staging system for childhood hepatocellular tumours does not exist. Through the various staging systems used, the different approaches to treatment adopted by the different study groups are reflected. The North American Co-operative Study Groups on HB favouring primary surgery, use a post-surgical staging system based on the results of
the initial attempt at complete resection of the tumour mass. Thus, four stages are identified:

- Stage 1: Complete resection, no microscopic residual disease.
- Stage II: Microscopic residual disease.
- Stage III: Macroscopic residual disease.
- Stage IV: Distant metastases.

This surgical staging system is in contrast to the one that was developed and used by the Liver Tumour Study Group of the International Society of Paediatric Oncology (SIOPEL), whose therapeutic strategy is based on primary chemotherapy. The PRETEXT system (pre-treatment extension of disease) is based on pre-treatment imaging with ultrasound, CT scans and MRI, and describes the site and size of the tumour, invasion of vessels, and distant spread, as judged. The system identifies four PRETEXT categories (I-IV) which reflect the number of sections of the liver that are free of tumour, and describes the extension of the disease beyond the liver using the following letters:

- 'V' if the tumour extends into the vena cava and/or all three hepatic veins.
- 'P' if the main and/or both left and right branches of the portal vein are involved by tumour.
- 'E' if there is evidence of extra hepatic intra-abdominal disease.
- 'M' if there are distant metastases.

**SIOPEL**

In 1983, a first draft of the SIOPEL protocol was written for the SIOP Scientific Committee, proposing a pilot study for liver tumors in children with the aim:

1. To assess the value of preoperative therapy on the resectability of liver tumors and
2. To monitor the various surgical techniques to obtain guidelines for safer major hepatectomies in children.

In 1987, at the SIOP meeting in Jerusalem a preliminary meeting took place of representatives from National Pediatric Oncological Societies interested in a cooperative study (France, Italy, Germany, Netherlands, UK, Sweden). And in December of that year, a questionnaire was sent out to inquire about the past experience, to see how many patients could be expected to be curable, and to see if there was enough common ground for an international co-operative study. In February 1988, the first SIOP Liver Tumour Study Working Party meeting was organized in London where the questionnaire was evaluated and the aims and scope of the study was formulated.

The second meeting was organized in June in the Institute Gustave Roussy in Paris where the preliminary working document was prepared under the chairmanship of Jack Plaschkes. That same year at the SIOP meeting in Trondheim, Norway, the document was discussed with other interested non-European country representatives and amended, and a protocol writing committee was formed. The third SIOP meeting was organized in February 1989 in Padua, Italy, where consensus was reached for the details of the final protocol that was written in its final form in March 1989 by the core committee chaired by Plaschkes. The pilot protocol was then introduced at the SIOP Scientific Committee meeting in Amsterdam in April, and was activated on July 1st, 1989. That same year in September, the protocol was introduced at the first IPSO meeting that occurred that year as a first full surgical symposium back to back with the SIOP meeting in Prague. (But it would take until 1991 that IPSO was officially founded at the Rhodes SIOP meeting in Greece). After 2 years of preparation and a short, limited institutional pilot trial, the SIOP Liver Tumour Study Group launched its first clinical study - SIOPEL 1 (SIOP Epithelial Liver 1) in 1990. This was the first full-scale, prospective, multinational clinical study of hepatoblastoma ever performed.

**General therapeutic strategies from the 1980s onward**

1. **Resection followed by chemotherapy or radiotherapy.**

In the United States, tumor resection at diagnosis, whenever possible, has been advocated with the arguments that toxicity of chemotherapy can be reduced by avoidance of unnecessary neoadjuvant chemotherapy, that some tumors may become resistant to prolonged courses of chemotherapy, and that the highest survival rates have historically been observed in patients with initially resected tumors, although these tumors also tend to be the smaller more favorable tumors. The currently proposed COG Surgical guidelines for the upcoming AHEP-0731 study advocate definitive surgical resection at diagnosis for localized, unifocal PRETEXT I and II tumors.
followed by chemotherapy. When the tumor is large (PRETEXT III or IV), multicentric, shows radiographic evidence of portal or hepatic venous invasion, or pulmonary metastatic lesions, it has been stated for the first time that the chance of curative resection may be improved with neo-adjuvant chemotherapy and delayed primary resection.21

2. Primary exploration and resection if ‘easy’. Otherwise treat with chemotherapy and do second look surgery.

The German Society for Paediatric Oncology and Hematology (GPOH) started its Hepatoblastoma study (HB89) in January 1989.20 The following strategy was chosen: a primary laparotomy was performed in all children with a liver tumour. Resection was only performed primarily in cases where this could be done with a sufficient margin by conventional partial hepatectomy. Tumours extending into both lobes of the liver were only biopsied, and treated with chemotherapy in the case of malignancy. A second look operation was carried out after two or three courses of chemotherapy, now with the aim to remove all tumour, even by using extended resection procedures. Chemotherapy consisted of a combination of ifosfamide, cisplatinum and adriamycin. In cases of insufficient tumour response, high dose cisplatin and adriamycin were added as continuous infusion, similar to the CCG 832 study. As second line therapy, carboplatin, VP 16, methotrexate and epirubicin were used. From 1988 to 1993 a total of 94 children with a primary liver tumour were included, followed by the HB 94 (n=69) and the HB 99 (n=100) study trying more intensified chemotherapy combinations to treat HR-HB. In 2008 after closure of HB99, GPOH decided to stop the HR-HB treatment with high dose carboplatin/etoposide, and will join the next SIOPEL HR-HB study.

3. Chemotherapy prior to the operation in all cases.

Several reports on pre-operative chemotherapy in the treatment of hepatoblastoma had already been published in the 1980s.22-26 This basically became the approach in the SIOPEL-I study. Patients were treated after biopsy with pre-operative PLADO (cisplatin-doxorubicin) and assessed for resectability after four or six courses. SIOPEL-1 was conducted between 1990 and 1994. A total of 91 centres in 30 different countries participated. Registered were 193 patients, 153 had hepatoblastoma and 40 hepatocellular carcinoma. 115 HB patients had delayed surgery, of whom 106 had complete resection (including p-OLT x6). Outcome: 5-year OS 75% (95%CI 68-82%) and 5-year EFS 66% (95%CI 59-74%) For hepatocellular carcinoma 20 never became resectable, and 14 (36%) had complete resection. Outcome: 5-year OS 28% (95% CI 14-43%), 5-year EFS 17% (95% CI 6-30%). Significant findings were that relapse rate for hepatoblastoma was low. Hepatocellular carcinoma patients did much worse in terms of relapse and mortality, and the role of chemotherapy is uncertain in this tumor. Transplantation should be considered for patients with unresectable tumour after response to PLADO, which should be performed in about 15% of cases.27,28


Yokomori and others from Tokyo have reported on complete disappearance of unresectable hepatoblastoma by continuous infusion of 5 FU, vincristine, adriamycin and cisplatin through the hepatic artery.29 Chemoembolization also has been reported as successful as rescue therapy.30

SIOPEL-1: lessons learned

SIOPEL-1 was the first study that used the concept of neo-adjuvant chemotherapy and delayed surgery. The study was designed as an international, prospective, single arm study, with informed consent from parents and/or patients. An open or closed biopsy was strongly recommended, and the pathology was centrally reviewed.

• Lessons learned 1 (Pritchard et al.)31 - the concept: International collaboration on a large scale is feasible. The toxicity of PLADO was acceptable and the overall survival was
gratifyingly high, which made PLADO + delayed surgery the standard treatment.

- Lessons learned 2 (Brown et al)\textsuperscript{32} - prognostic factors: OS and EFS were univariately associated with PRETEXT and presence of metastasis; tumor focality and enlargement of hilar lymph nodes were univariately associated with EFS. PRETEXT and metastasis were predictors of EFS. Multivariately, PRETEXT was the only predictor of OS.

- Lessons learned 3 (Perilongo et al)\textsuperscript{33} - metastases at diagnosis: The SIOPEL strategy seemed to cure 25% of patients who present with lung mets, alternative chemo and (repeated) thoracotomies can save another 25% of these patients.

- Lessons learned 4 (Schnater et al)\textsuperscript{34} - surgical analysis: pre-operative PLADO decreased resection size in 28% of patients; biopsies are safe; partial hepatectomy with microscopic residual at the resection margin may still be curative; resection of lung metastasis can be curative, but should only be performed after local tumor control has been achieved; surgery carried a morbidity of approximately 20%.

- Lessons learned 5 (Otte et al)\textsuperscript{35} - liver transplantation: LTx should be considered in every child with unresectable HB (approx. in 15% of cases), but extrahepatic viable tumor deposit, not amenable to excision, is regarded the only contraindication. Patients with lung metastases at diagnosis are eligible for LTx if metastases cleared completely after chemotherapy and/or metastasectomies. Positive response to preop chemotherapy is mandatory. LRLTx guarantees optimal timing of surgery. Extensive HB should be treated in specialized centers.

- Lessons learned 6 (Aronson et al)\textsuperscript{18} - validation of pretext: Accuracy of PRETEXT is moderate (due to difficulty to distinguish compression from ingrowth), with a tendency to overstage. Good interobserver agreement exists. The predictive value for survival is superior to the other staging systems. Advantages of PRETEXT are: the stage-ability of the non-surgical patient, and the possibility to monitor the effect of neo-adjvant therapy.

- Lessons learned 7 (Czauderna et al)\textsuperscript{36} - HCC: survival HCC is significantly worse than HB; complete excision offers the only realistic chance for cure; the disease is often advanced at diagnosis; presence of metastases is a potent predictor of poor outcome; novel therapeutic concepts are needed.

**Current challenges**

**Risk stratification**

Before treatment, both the extent of intrahepatic disease, as defined by the pre-treatment extension of disease (PRETEXT) system, and the presence of lung metastases were identified as prognostic factors for 5-year event-free survival (EFS), but in multivariate analysis the PRETEXT category was the only statistically significant prognostic factor for 5-year overall survival (OS). Based on these findings, the SIOPEL group decided, for the subsequent SIOPEL-2 trial, treatment according to risk stratification.\textsuperscript{37} Standard risk (SR-HB), defined as tumour confined to the liver, involving at the most 3 hepatic sectors, and AFP >100 ng/mL would be treated with cisplatin monotherapy. High risk (HR-HB), defined as tumour involving all 4 liver sectors (PRETEXT -IV) or vascular invasion (V+P+) or extra-hepatic disease (E+/M+) or low alpha-fetoprotein (AFP<100 µg/L) at diagnosis or tumour rupture, was treated with intensified chemotherapy, called SUPERPLADO (CDDP-Carbo-Doxo). The protocol also encouraged to perform liver transplantation in unresectable tumors.

**Advanced tumors / judgement of resectability**

Liver transplantation (LTx) has added a new dimension to the treatment of HB.\textsuperscript{36,38} LTx is a good treatment option in children with unresectable primary tumors and without demonstrable metastatic disease after neoadjuvant chemotherapy, and pulmonary metastasectomy if necessary. In large solitary, and especially multifocal, hepatoblastomas invading all four sectors of the liver, transplantation has resulted in long-term disease
free survival in up to 80% of children. LTx should therefore be considered for every child presenting with unresectable disease due to involvement of all four sectors of the liver or involvement of three sectors when a complete tumor excision, by partial hepatectomy, is unlikely. The only absolute contraindication to LTx is the persistence of one or more 'viable' extrahepatic deposits after chemotherapy that are not amenable to surgical excision. Extension into the major liver vessels might not contraindicate LTx as long as all tumors can be excised at the time of hepatectomy. Chemotherapy must be given before LTx.

**Tumor recurrence**

The prognosis for a patient with recurrent or progressive hepatoblastoma depends on many factors, including the site of recurrence, prior treatment, and individual patient considerations. For example, in patients with stage I hepatoblastoma at initial diagnosis, aggressive surgical treatment of isolated pulmonary metastases that develop in the course of the disease may make extended disease-free survival possible.\(^{39}\) If possible, isolated metastases should be resected completely in patients whose primary tumor is controlled.\(^{34,37}\) In recurrent refractory disease, phase I and II clinical trials may be appropriate and should be considered.

The prognosis for a patient with recurrent or progressive hepatocellular carcinoma is poor. Phase I and II clinical trials may be appropriate and should be considered.

**Ototoxicity**

Both SIOPEL and COG have put considerable effort in trying to decrease the significant ototoxicity induced by the use of cisplatin-based chemotherapy in young patients. The COG 9645 trial failed to reduce ototoxicity with the agent amifostine.\(^{40}\) The recently opened SIOPEL-6 study will investigate sodium thiosulfate\(^{41}\) as an attempt to decrease the cisplatin induced ototoxicity.

**SIOPEL-2: (pilot) and SIOPEL-3**

Data from the recent risk stratified SIOPEL-3 study showed for SR-HB (n=255) that cisplatin monotherapy was as effective as PLADO in terms of complete resection rate; these two regimens achieved comparable 3-year EFS and OS rates (CDDP: EFS 83% [95%CI 77-90%], OS 95% [95%CI 91-99%] with a median follow-up time of 45 months). Cisplatin alone was less toxic than PLADO.\(^{42}\) For HR-HB (n=158) it was shown that compared to SIOPEL1 (3y-PFS 45% [95%CI 32-56%]; OS 67% [95%CI 55-80%]) this platinum-intensive regimen has significantly improved DFS in high risk HB [3y-DFS and 3y-OS for all HR-HB patients: 65% (95%CI 57-73%) and 73% (95%CI 66-80%)]. LTx was performed in 35 (22%) patients. Patients with low AFP still have a very bad prognosis.\(^{43}\)

**International developments - the CHIC project**

In 2007 SIOPEL and COG decided to embark on a mutual project that was called the Childhood Hepatic tumors International Collaboration (CHIC). The complete databases of both groups are in the process of being united in order to be able to address mutual questions, like 'Can we identify common risk stratification criteria?' In order to identify these common data points for prognostication and risk stratification, data regarding prognostic factors (i.e. histology, AFP, stage, multi-focality, biologic markers, etcetera) can thus be studied in much larger patient groups in which the clinical outcome is known. These developments show the starting point of a new transatlantic converging co-operation on a large intercontinental scale, that will be of eventual benefit for children with liver tumors.

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Medulloblastoma: Current treatment strategies and perspectives

Stefan Rutkowski

Abstract
Survival rates of medulloblastoma, the most frequent malignant brain tumor of childhood, have improved significantly in most treatment groups which are still defined by the clinical risk factors age, postoperative residual tumor dissemination in most of the current clinical studies. Around 80% of average risk patients older than 3 years, treated by postoperative craniospinal radiotherapy and maintenance chemotherapy, remain relapse-free 5 years after diagnosis. Survival rates have been increased in children with metastases of the same age-group up to 60% by intensified adjuvant treatment concepts. After survival rates of young children with medulloblastoma have been well below 50% and static for decades, significant progress has been achieved by recent clinical studies using different strategies aiming to avoid craniospinal irradiation in non-metastatic disease. At young age, postoperative residual tumor has been identified as adverse risk factors, and desmoplasia has been shown to be a strong favorable prognostic factor. Merely all treatment strategies currently for children with medulloblastoma are potentially causative for neurocognitive, behavioral and neuroendocrine long-term deficits and secondary malignancies. In future, prognostically relevant biological markers may be incorporated in clinical trials to further improve the risk-dependent stratification in patients with medulloblastoma.

Introduction
Medulloblastoma, the most frequent malignant brain tumor of childhood, is an invasive embryonal tumor of the cerebellum with an inherent tendency to metastasize via the subarachnoidal space\(^1\). In the first year of life, medulloblastoma is the most common tumor in the posterior fossa, and about 50% of medulloblastomas are diagnosed in children younger than 5 years\(^2\). Up to 60-80% of children older than 3 years at diagnosis can be successfully treated using the current therapeutic strategies, including neurosurgical resection, radiotherapy and chemotherapy, but significant tumor- and treatment related side effects have to be considered\(^3\). In the last decades, stratification of patients to risk groups has been based on age, staging and presence or absence of significant postoperative residual tumor\(^4\).

Histology and biology
Medulloblastoma is an embryonal tumor originating from pluripotent primitive neuroectodermal cells of the cerebellum. Most medulloblastomas arise spontaneously from the roof of the fourth ventricle. Most medulloblastomas arise spontaneously from the roof of the fourth ventricle. Histologically, desmoplastic medulloblastoma (DMB) can be distinguished from classic medulloblastoma (CMB) and other variants. Cytological variation in medulloblastoma has led to the concept of the large-cell anaplastic medulloblastoma, believed to be associated with a poorer prognosis on one side, and DMB together with medulloblastoma with extensive nodularity on the other end of the spectrum\(^5\). DMB is characterized by nodular reticulin-free zones (pale islands) surrounded by densely packed, highly proliferative cells that produce a dense intercellular reticulin fiber network. Classic and anaplastic histological subtypes are believed to arise from the ventricular matrix of the fourth ventricle via activation of the WNT pathway, LOH 17p, and amplification of the protooncogene myc. In contrast, desmoplastic medulloblastoma subtypes may arise from the external granular layer in relation to the hedgehoc pathway and LOH 9q22\(^6\). Desmoplastic and classic medulloblastomas have distinguishable gene expression profiles with potential prognostic relevance. There is growing evidence that DMB is not rare in younger childhood: A relatively high proportion of children with DMB (47%) was found in the a German study, and the promising survival
rates observed were predominantly related to children with DMB compared to children with the classical subtype (PFS 85% vs. 34%). Desmoplastic histology was identified as a favourable independent prognostic factor in that study. The observations on the frequency and on the prognostic relevance of desmoplastic histology in young children with medulloblastoma have been confirmed in a metaanalysis on 5 national study groups.

Four distinct medulloblastoma variants that can be reliably identified histologically and that have some relevance on clinical outcome, have been defined in the latest WHO classification in 2007: 1) Desmoplastic/nodular medulloblastoma, 2) medulloblastoma with extensive nodularity, 3) anaplastic medulloblastoma, and 4) large cell medulloblastoma.

Mutations of the WNT- and SHH pathways, both involved in medulloblastoma tumorigenesis, have been predicted by gene expression profiling and related to prognostically different subgroups.

Different signalling pathways and genes have been shown to be altered in medulloblastoma: The WNT pathway, also involved in Turcot's syndrome, is altered in around 15% of children with medulloblastoma. Several studies have shown that β-catenin is a robust biological marker for activation of the WNT pathway in association with a better clinical outcome, which may be subject to targeted selectively in future. The other well described pathway, the sonic hedgehog pathway (SHH), altered predominantly in desmoplastic medulloblastoma, also offers effective strategies for targeted therapies.

Other candidate molecular markers have been investigated retrospectively for their potential prognostic relevance. Amplification and mRNA expression of the proto-oncogene c-myc and expression of ERBB2 have been associated with an unfavourable prognosis.

**Diagnosis and staging**

The local extent of infiltration to the floor of the fourth ventricle and to the cerebellar-pontine angle frequently determine the presence of focal neurological deficits and the feasibility of the recommended maximal safe neurosurgical respectability, but initial clinical symptoms are often related to hydrocephalus occlusus. Due to an inherent tendency to spread along the neuroaxis via the subarachnoidal space, cranial or spinal metastases can be detected in about 30 percent of patients at diagnosis. The Chang classification system, based mainly on the extent of the primary tumor, on macroscopic metastases diagnosed by craniospinal MRI, and on dissemination of tumor cells into the cerebrospinal fluid (CSF) has been broadly accepted for staging.

Other histological entities such as atypical teratoid rhabdoid tumors, a highly malignant embryonal tumor which has been defined in the last decade and especially frequent in very young children, and ependymomas or astrocytomas, must be distinguished from medulloblastoma.

**Treatment**

Most primary tumors can be resected at least subtotally using modern imaging and surgery techniques. However, more than 20% of children, especially in those with brainstem invasion, develop a more or less severe posterior fossa syndrome (cereballar mutism syndrome) with diminished speech, emotional lability, hypotonia, and ataxia which may persist in a significant portion of children over time.

Medulloblastoma is traditionally regarded as sensitive to chemotherapy and radiotherapy. Metastatic disease and postoperative residual tumor have been identified as adverse risk factors older than three years at diagnosis. In this age group, survival rates have been improved by combined strategies using craniospinal radiotherapy and polychemotherapy regimens, reaching 5 year progression-free survival (PFS) rates of 60-80%. The application of postoperative radiotherapy followed by maintenance chemotherapy has been shown to be superior compared to neoadjuvant sandwich chemotherapy followed by irradiation. The dose of craniospinal irradiation has been reduced successfully from 36 Gy to 23.4 Gy in combination with maintenance chemotherapy (cisplatinum, vincristin and CCNU or cyclophosphamide). Further deescalations of radiotherapy (craniospinal irradiation dose and irradiation field within the fossa posterior) are currently investigated prospectively.
Improved survival rates of 50-75% have also been obtained for children with poor-risk medulloblastoma using higher doses of post-irradiation chemotherapy\textsuperscript{12,17}.

Treatment of early childhood medulloblastoma constitutes a particular challenge, because of special concerns to expose young children to therapies associated with potential risks of early neurotoxicity and subsequent deficits in cognition, growth and endocrine functioning. The increased susceptibility of the immature brain to radiotherapy-induced cognitive deficits\textsuperscript{18} has set age limitations on the use of radiotherapy in children younger than 3 years, and survival rates for with medulloblastoma treated by surgery, chemotherapy and radiotherapy did not exceed 25% to 45% until the last decade\textsuperscript{19}.

Different treatment strategies are currently used by different national groups, all with the potential to improve survival rates of localized early childhood medulloblastoma: Intraventricular chemotherapy was newly added to systemic chemotherapy to substitute radiotherapy. Progression-free survival was higher than 80% for children without metastases and without residual tumor\textsuperscript{7}. Neurocognitive functions of children were better compared to children from a previous study who received craniospinal irradiation. The SFOP investigated the role of protracted postoperative chemotherapy alone to replace radiotherapy in young children with medulloblastoma, and only patients with relapse or tumor progression received high-dose chemotherapy and stem-cell transplantation followed by local or craniospinal radiotherapy as salvage treatment. A small portion of non-metastatic medulloblastoma patients with complete tumor resection were treated efficiently by this induction chemotherapy\textsuperscript{20}, but a significant portion of children with completely resected localized disease was salvaged successfully by high-dose chemotherapy and radiotherapy (5-year OS 73% for this subgroup).

Two other studies using different strategies have been closed recently, using either intensive induction chemotherapy followed by myeloablative high-dose chemotherapy with stem-cell transplantation (CCG 99703) or systemic chemotherapy, second-look surgery, and conformal radiotherapy to the posterior fossa and primary site, followed by maintenance chemotherapy (COG P9934, for children with localized medulloblastoma). More intensified treatment regimen may be required for the high-risk group of young children with metastatic medulloblastoma.

### Late effects

All treatment strategies currently adopted in young children with medulloblastoma are potentially causative for neurocognitive, behavioral and neuroendocrine long-term deficits. A significant portion of long-term medulloblastoma survivors have limitations of social integration and every day-life.

Particularly in young children, craniospinal irradiation results in irreversible dose-related morbidity including neurocognitive and neuroendocrine deficits and impairment of bone and soft-tissue growth. Loss of IQ has been shown to be progressive over at least one decade after radiotherapy, and mean losses of 2-4 IQ-points per year have been reported\textsuperscript{21}. An association of craniospinal radiotherapy with declines in academic abilities, social skills, attention and reading has been demonstrated.

Older children treated with reduced-dose craniospinal radiotherapy (23.4 Gy) had substantial IQ loss, but to a lesser extent than children treated with higher craniospinal dose. There is some evidence that neurocognitive deficits are less pronounced in children after local radiotherapy to the posterior fossa or confined to the tumor bed in young children with brain tumors\textsuperscript{22}.

Among others, potential causative agents of secondary malignancies are alkylating agents, etoposide, and irradiation. A large study on children younger than 3 years with primary brain tumors treated with postoperative chemotherapy and delayed radiotherapy reported a cumulative risk at 8 years of 11.3% to develop secondary malignancies\textsuperscript{23}. Survivors of studies on children with medulloblastoma need a long follow up for secondary malignancies.

### Outlook

Consequently, new stratification criteria combining clinical, histological and molecular risk factors have been proposed, aiming to improve risk-adapted treatment recommendations in future. Favourable risk patients may be stratified to receive less intensive radiotherapy or chemotherapy. Furthermore, high risk patients may be identified at diagnosis.
as candidates for more intensified primary treatment regimens. Central sampling of snap-frozen and formalin-fixed tumor samples should be routinely included in modern clinical medulloblastoma trials.

New experimental treatment strategies, such as immunotherapy, antiangiogenic therapy, gene therapy, and modern drug delivery systems (liposomal encapsulation, convection enhanced delivery) may become relevant for clinical evaluation.

References

“Trying to be a Good Parent to my Dying Child”: The Basis of Parental End-of-Life Decision Making in Pediatric Oncology

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Introduction

Parents/guardians of children with incurable cancer face end-of-life decisions on behalf of their child including whether or not to enroll their child in a Phase I study, agree to a ‘do not resuscitate’ status, or to begin terminal care. Descriptive research to date indicates that one of the factors that most helps parents to make these decisions and to remain satisfied with the decision afterward is their perception that they decided as a ‘good parent’ would decide. We describe here a construct, ‘being a good parent to my dying child,’ that is derived from a series of end-of-life decision making studies and other relevant literature and is the basis of parental end-of-life decision making. This construct appears to have great importance during and following the child’s end of life as parents of children with incurable cancer report that their sense of having been ‘a good parent’ at the end of their child’s life directly helps them to emotionally survive the dying and death of their child.¹

Parents define being a ‘good parent’ as acting in a way they perceive to benefit their child, even if it requires considerable self-sacrifice. These parents report end-of-life decisions to be the most difficult decisions they faced during their child’s treatment². How staff members react to these decisions (conveying respect or doubt to parents) influences parents’ sense of their own competence at a time when there are few remaining opportunities to function as their child’s parent. Staff reactions also influence parents' trust of staff at a time when trust is essential to fully meet the needs of the dying child and the family. Staff members who are inadequately informed of the basis for the parents’ decision may, in their role as patient advocates, directly question the parents’ decision or indirectly convey doubt about it. Parents report that they interpret this questioning behavior to indicate that staff doubt their ability to make good decisions on behalf of their child and therefore to function as ‘good parents’ at this point in their child’s life³.

Staff tension can result from individual efforts to be patient/family advocates. Advocacy for some staff includes taking steps to be certain that the patient and family are fully informed of treatment options and the likely consequences of their options, and that the patient and family fully understood the information given to them. Lack of adequate information about the end-of-life treatment decision making can also create staff tension. This tension is attributed in part to the impossibility of all staff involved with the patient’s care being able to be present during end-of-life discussions and thus not being able to know first hand about the actual discussion and decision making. Staff are more likely to be comfortable with and supportive of parents’ end-of-life decisions when staff are well informed about the decision and the parents' rationale for that decision, and when staff and parents agree about the decision and its meaning⁴.

An intervention that makes explicit the parent’s definition of ‘a good parent' in the end-of-life decision-making process and communicates that definition and the rationale for the parent's decision to staff could reduce parental self-doubt during and after the decision process and reduce staff tension about the parental decision.

The long-term goal of our research program is to develop and implement a clinical intervention that a) helps parents to fulfill their definition of a ‘good parent' at the time of end-of-life decision making for their child, b) reduces the likelihood that parents will doubt their decision, and c) reduces staff tension about the end-of-life decision.
Historical Perspective on End-of-life decision making in Pediatrics

A remarkable shift has taken place during the last decade in the philosophy of parental (and child, when possible) involvement in decisions about medical treatment, including end-of-life decisions. This shift is represented formally in the policy statements of professional organizations, including the American Academy of Pediatrics, the American Nurses Association, and the Society of Critical Care Medicine. Although the expectation that parents should be involved in medical decision making is made explicit, the guidelines for doing so are not. Single-site studies conducted primarily in North America or Europe have described the decision making of parents of seriously ill neonates, of parents of children facing surgery, of parents of children with chronic illness, of parents of critically ill children in an intensive care unit, and of parents of terminally ill children. Parental treatment-related decision making has been investigated primarily through reviews of medical records, and to a lesser extent by semi-structured interviews and questionnaires. Collectively, study findings indicate that parents are influenced by the way in which information is presented to them, their desires to be 'good parents', and the preferences of the healthcare team. In the process of end-of-life decision making, first the health care professionals present all medically viable options to the family and, in some situations, the pediatric patient. Parents and patients then choose among the legitimate options. In making this choice, parents have the ultimate authority. When staff accept the legitimacy of the medical options and are adequately aware of the parents' (or patient's) choice and of the rationale for the choice, they are more likely to recognize the parental (or patient) authority in making the decision and are less likely to experience discord with co-workers about the decision or to convey doubt about the decision to the family.

End-of-Life Decision Making in Terminally Ill Pediatric Patients

The available reports on end-of-life decision making that involve both parents and healthcare providers are predominantly from neonatal settings. End-of-life decisions in these settings often reflect the presenting condition of the infant. Most reports describe the decision making as having been initiated when the intensivist determined that the infant had no chance for survival or no chance for quality of life. In most cases, parents agreed with the recommendations of the intensivist or the infant's attending physicians. These descriptive reports are based on review of medical records and not on parent report. Two notable exceptions exist. In the first, Able-Boone and colleagues interviewed parents and healthcare providers of seriously ill infants about medical decision making and the provision of healthcare information. The parents emphasized their need and desire to be honestly informed of their child's health status. Parents also expressed a strong need for information to be coordinated by the healthcare team so that the information given to them was not confusing or contradictory. The second study that recorded the values of parents in end-of-life decisions was a grounded theory study in which Rushton interviewed 31 parents of 20 hospitalized neonates with life-threatening congenital disorders about their decisions for or against implementing or continuing life sustaining measures for their infant. Rushton concluded that the parents were guided in these decisions by their understanding of what it means to be a 'good parent' of a neonate with a life-threatening congenital disorder. According to these parents, the characteristics of good parents of such neonates include putting the needs of the neonate first, not giving up, not taking the "easy" way out despite the self-sacrifice involved, and having the courage to pursue a "good outcome" for the child.

Parents of children with incurable cancer have described being inexperienced in making treatment-related decisions because their child had been treated on a therapeutic protocol in which care was predetermined. Only when cure was no longer an achievable goal did parents make choices about their child's care options and outcomes. Our end-of-life studies indicate that most parents prefer to make the decision in collaboration with the health care team. When parents prefer to be involved but lack decision making experience, their ability to live up to their definition of a good parent is threatened, and their discomfort can be great enough to
negatively affect their view of their interactions with the health care team.

**Being a Good Parent of a Critically Ill or Dying Child**

The contribution of parents to a child's moral, physical, emotional, and mental development has long been studied. Parental contributions are judged by socially and morally defined standards. The notion of being a 'good parent' has been less well studied. It appears to be more individually defined, although it is doubtlessly affected by societal views. In the previously cited study by Rushton, participating parents evaluated themselves and their actions on the basis of their definition of a 'good parent'. The decision making process was influenced by uncertainty, ambivalence, parents' search for meaning, and certain external factors. Rushton's work helped to explain the process that parents of a critically ill or dying infant use to make a decision and how factors that interfere with their efforts to adhere to their definition of a 'good parent' can negatively affect their view of themselves and/or of others, such as health care providers. The definition of a good parent was internal to the participating parents, many of whom were not aware of it until a clinical or family event brought it into awareness. Therefore, health care providers were also unaware of this important internal definition or standard and thus were unable to support parents in achieving it. In other qualitative studies, parents whose child had died of cancer were asked through open-ended interview questions about the experience of caring for their dying child. A common theme revealed in these studies was the parents desire to retain parenting responsibility for their dying child. 20, 21.

**End-of-Life Communication Interventions**

Communication between the health care team and parents of dying children has been identified in several reports as the primary factor in preparing parents for the death of the child and for adequately managing the child's difficult symptoms. Parents report that they want reassurance that they and the health care team have done all that could be done for the child and that what has been done was done as well as possible. These reports suggest that health care professionals are in a key position to assist parents in fulfilling their 'good parent' definition. Indeed, parents of seriously or critically chronically ill children have identified their need for "affirmational support," or reassurance that they are caring well for their ill child. This type of support includes the important aspect of

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**Fig 1:** Model of Pediatric Quality of Life at End-of-Life: Dual Focus on the Dying Child or Adolescent and His Family
recognition from health care providers of the parents' efforts to act wisely on behalf of their child. Parents also report that their relationship with staff is strengthened by openness, willingness to provide accurate information and frequent updates, and sympathetic delivery of information. Conversely, ineffective communication can leave parents feeling angry or responsible for their child's death.

Conceptual Model Underlying this Research:

The conceptual model underlying this research program (Figure 1) evolved from the St. Jude descriptive studies on end-of-life decision making and from other published studies on pediatric and family end-of-life experiences. The parents of pediatric cancer patients report perceiving a prolonged, intense, and focused effort to cure their child's disease. According to the parents, there is a seemingly abrupt transition from the intense focus on curative care to end-of-life care after the child's disease becomes incurable. Parents experience this transition as extraordinarily difficult and painful; at times they are able to openly acknowledge the transition, but at other times they purposely avoid discussing or consciously acknowledging it. Parents experience this transition as extraordinarily difficult and painful; at times they are able to openly acknowledge the transition, but at other times they purposely avoid discussing or consciously acknowledging it. Parents sense the transition of their child's care from a curative to an end-of-life focus at different points; the exact timing is influenced by a number of factors. A central factor is parents' awareness of the child's symptoms. Changes in their child's appearance or body are particularly powerful indicators of their child's decline. Parents report that when their child is on a ventilator, they are less able to detect symptoms that would help to warn them of their child's approaching death. Parents of non-ventilated children point to the physical, mental, and emotional changes in their child that help to warn them of the transition and perhaps of impending death. Parents report being influenced in their efforts to be good parents by their child's symptoms; as 'good parents,' they may seek to end their child's suffering by choosing to end treatment efforts or by choosing to pursue aggressive therapy. A major factor in their awareness and interpretation of the symptoms is information from their child's healthcare providers. Parents report relying on the detailed interpretation offered by physicians, nurses and others on the healthcare team about their child's health status. Parents rely particularly on the attending physician for information about the likelihood of survival and the current status of their child's body systems. The trust relationship between the parent and the health care team is of prime importance to the parents as they interpret the information given to them by the physician and other team members. The interaction of these decision making factor can ultimately facilitate a focus on quality of life for the patient and for the family at the child's end of life. In sum, the concept of a 'good parent' has a great influence on the parents' end-of-life decision making. Parents prefer, when possible, to reflect their child's preferences in their 'good parent' decision making and to receive positive feedback from staff about the wisdom of their decision and staff acknowledgment that they are capable of making good decisions at the end of their child's life.

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Abstract

The ~20,000 protein-encoding RNAs are transcribed from ~1% of the genome. Until recently, it was assumed that the other 99% was ‘junk’ DNA from which no RNA was transcribed. Recent work, notably the ENCODE Project (ENCYclopedia Of DNA Elements), clearly shows this premise to be false. On the contrary, over 90% of the DNA genome appears to be transcribed into RNA. It is now becoming clear that some of these transcripts are used to create alternate exons and exon boundaries in protein encoding genes (thereby increasing the potential complexity of protein gene products by an order of magnitude). Even accounting for these RNA transcripts, the remainder accounts for the majority of RNA transcription in the human genome. Some of these are now well known (such as miRs), but most are simply described as non-coding RNAs with largely unknown function. It is now clear that many if not most of these have an important regulatory function and play an important role in the pathogenesis of cancer.

What is a Gene?

Until recently, genes were considered synonymous with RNA transcripts that encode a protein, based on the central paradigm of molecular biology: DNA encodes RNA that is translated into protein. Using that criterion, it was surprising that upon completion of sequencing of the human genome, only about 20,000 annotated genes were identified, more or less the same number found in organisms like C. elegans. Clearly, the sheer number of genes in an organism could not begin to explain the extraordinary differences between a worm like C. elegans and humans, for example. This in turn led to a lengthy debate as to what constitutes a gene, particularly in view of data that emerged from a multi-year, multi-investigator
effort to define an 'encyclodpedia' of DNA encoded RNA elements (the ENCODE project).(Thomas, Rosenbloom et al. 2007) From the original concept of a gene as a distinct unit of heredity, through genes as discrete loci, blueprints for proteins, a physical entity within the genome, a transcribed code, an open reading frame (ORF), and most recently a gene as an annotated entity (RefSeq, Ensembl, etc.), the current concept of a gene as a sub-routine in a complex genomic 'operating system' (analogous to a computer OS) has emerged. (Gerstein, Bruce et al. 2007) In this context, a gene can be many things besides a protein encoding hereditary unit. In point of fact, non-coding RNAs have been known for decades, notably ribosomal RNAs, transfer RNAs, small nucleolar RNAs, and even 'genes' like H19, whose role is to regulate expression (or not) of IGF2, notably in tumors like Wilms' and embryonal rhabdomyosarcoma.(Anderson, Gordon et al. 1999; Feinberg 1999; Lynch, Tycko et al. 2002; Astuti, Latif et al. 2005) The important difference here is the sheer number of newly recognized, non-coding RNAs, and the associated concept of these transcripts as functional, regulatory elements, most of unknown function.

**Genome-Wide RNA Transcription**

A major consequence of the publication last year of the data from the ENCODE project was an appreciation of the near-genome wide transcription of RNA that occurs constantly, from both strands of the double stranded DNA.(Birney, Stamatoyannopoulos et al. 2007) Detectable levels of transcription are estimated to occur from well over 90% of the 3.3 billion bases in the human genome (based on the 1% of the genome that was analyzed by ENCODE in great detail), as illustrated in figure 1. That number rises to 6.6 billion when transcription from the negative strand is included. In addition to the sheer number of RNA transcripts that were detected (which obviously can not even begin to be accounted for based on known protein-encoding genes), the most remarkable finding was the diversity of transcription start sites as well as novel exon usage and rather fluid exon boundaries. Taken together, the transcriptome ceases to be a simple 'read' of conventional exons following a 5' transcription start site, usually downstream of one or more promoter regions. Instead, it appears that some degree of RNA transcription can occur from virtually any part of the DNA genome, and the final form of a given messenger RNA varies widely.

**Fig 2:** Current Concept of a Protein-encoding Gene locus, with alternate splicing and variable exon boundaries illustrated.
Alternate Splicing & Fluid Intron-Exon Boundaries

Perhaps the single greatest contribution to diversity (and complexity) of the transcriptome arises for novel usage of known (and previously unknown) exons. The most common form of this is variable exon usage, leading to so-called 'splice variants', or alternate splicing (AS). Some simple arithmetic gives one an idea of the magnitude of this contribution to the complexity of the human transcriptome: an average annotated gene is composed of about 10 exons. If there are about 20,000 annotated genes, that accounts for about 200,000 exons. However, it is estimated that even protein encoding genes account for about 600,000 exons, and the average gene has at least six splice variants. Add to this the frequent observation that exon sequences themselves are often discrepant between reported mRNA sequences and it becomes apparent that intron-exon splice junctions are also variable, leading to variable amino-acid coding sequences as well as variable 5' and 3' untranslated regions (UTRs). This concept of variable exon usage and intron-exon boundaries is illustrated in figure 2, and is apparent with even superficial scrutiny of genes as portrayed in the UCSC Golden Path genome browser (http://genome.ucsc.edu/cgi-bin/ hgTracks). Thus, even conventional genes are highly variable, to an extent never imagined until publication of the ENCODE data. (Denoeud, Kapranov et al. 2007; Kapranov, Willingham et al. 2007; Trinklein, Karaoz et al. 2007) In addition, it has become increasingly difficult to determine whether a multi-exon RNA transcript is even a functional, protein encoding gene or a pseudogene, given this complexity. (Rozowsky, Newburger et al. 2007; Zheng and Gerstein 2007)

Non-Coding RNAs

While the above observations clearly implicate hundreds of thousands of RNA transcripts in the known protein encoding gene world, they still focus on a gene-centric world. Clearly, if genes as we previously understood them account for only 1.2% of the DNA genome, even allowing for widespread transcription variation, there must be a vast amount of RNA transcripts that are not structurally linked to conventional protein encoding genes. These areas of transcriptionally active regions (or TARs) were readily identified by the ENCODE consortium and are widespread throughout the genome, transcribed from either DNA strand, often some distance from any known annotated gene. (Thurman, Day et al. 2007) (Costa 2005; Costa 2007) Although the number of such non-coding RNAs (ncRNAs) is unknown, it is likely that in sheer number and volume they account for the majority of RNA transcription from the human genome. In silico prediction models predict at least 35,000 such ncRNAs, but the true number is likely far larger, depending on biologically relevant levels of transcription and functional consequence. By this measure, there is no reliable number of relevant ncRNAs. The real question, of course, is what the functional ones do, and how they do it.

Micro RNA (miR, miRNA)

By far the best-characterized family of ncRNAs are micro RNAs, or miRs. These 21-24 base transcripts have garnered a vast literature in the few years since their description in humans, and a Nobel Prize for those who discovered them. More importantly, numerous reports have appeared in that time frame elucidating not only their function in the (generally) negative regulation of protein-encoding genes, but more relevant to the topic at hand, their central role in oncogenesis and maintenance of the transformed state of tumor cells. A recent search of the literature identifies more than 600 publications documenting some aspect of miR expression in cancer (PubMed: miR & cancer). Many have been described in hematopoietic malignancies (including childhood leukemia) (Marcucci, Radmacher et al. 2008) and tumors in general (Lu, Getz et al. 2005), to the extent that miR profiles have been proposed as a means of classifying human malignancies.(Lu, Getz et al. 2005; Hernando 2007) An example of this is shown in figure 3, where patterns of miR expression unique to Ewing's sarcoma are illustrated. Perhaps even more importantly, the mechanism of miR action within known tumorigenic pathways like the p53 pathway are being elucidated, with the realization that miRs can mimic the functional consequences of p53 mutation or loss, for one example. (He, He et al. 2007) In other cases, expression patterns in normal development are mimicked by their tumor counterpart, as in childhood
neuroblastoma, where miR 34-a has been shown to be a tumor suppressor gene that suppresses tumor cell growth and induces apoptosis in neuroblastoma cells via E2F and BCL2, respectively. Further, when miR 34-a, located on chr 1p36, is deleted, MYCN expression is elevated and tumor growth is enhanced, thus elucidating a mechanism whereby miR 34-a suppression of MYCN leads to decreased cell growth and increased apoptosis. (Welch, Chen et al. 2007; Cole, Attiyeh et al. 2008; Schulte, Horn et al. 2008; Wei, Song et al. 2008)

Comparable studies of the role of miRs in other childhood cancers are lacking, and among the few such studies published to date, there was no identifiable role for miR 17-92 (located in the chr13q amplicon found in some rhabdomyosarcomas) in the clinical aggressiveness or outcome of pediatric rhabdomyosarcoma, as opposed to glypican-5, also located in the amplicon, which was strongly associated with outcome. (Williamson, Selfe et al. 2007)

Anti-Sense Transcripts

Another major class of ncRNAs is the group of RNA transcripts transcribed from the anti-sense strand of annotated genes, often near the 3’ end of the gene. (Kapranov, Willingham et al. 2007) These transcripts appear to exert a negative regulatory effect on the gene in question, not unlike miRs that frequently bind to the 3’UTR of a mRNA, leading to premature degradation of the transcript and reduced translation into protein. MiRs differ from the anti-sense transcripts, however, in that they are generally transcribed from other regions of the genome and can have diverse effects, by virtue of their ability to hybridize to hundreds of annotated genes across the transcriptome. Anti-sense transcripts, in contrast, typically target the gene encoded from the opposite strand. A particularly well known example of this is MYCNOS, the MYCN counterpart gene transcribed from the opposite strand in MYCN-amplified childhood neuroblastoma. MYCNOS (also known as N-cym) is expressed at high levels when MYCN is amplified and expressed at high levels. This is illustrated in figure 4, where exon-level RNA expression from both strands of DNA around the MYCN locus is illustrated. The implication is that MYCNOS regulates (or attempts to regulate) MYCN, thus qualifying as a regulator ncRNA of the anti-sense class. (Scott, Elsden et al. 2003)

Longer Non-Coding RNAs

While a critical role for short, less than 28mer RNAs (both miRs and siRNA) has been well documented in cancer and development, these moieties account for a small percentage of the total transcriptome. (Kapranov, Willingham et al. 2007) Given that only about 500 miRs have been described, covering a minute fraction of the genome, yet over 90% of the genome is transcribed at some level, it is clear that there are a vast number of longer RNA transcripts of largely unknown function (termed TUFs, or Transcripts of Unknown Function by the ENCODE project). (Cheng, Kapranov et al. 2005)

Further, these transcripts often overlap one another, and may incorporate exons from disparate sites in the genome, and even different gene exons (i.e., trans splicing). (Kapranov, Willingham et al. 2007) The picture that emerges from these data is a DNA genome from which a bewildering variety of nearly universal RNA transcriptional activity occurs on a continuous basis, with subsequent incessant processing, splicing, degradation, and hybridization to other RNA transcripts, leading to their up or down regulation.
regulation, degradation, and modulation of translation. This is clearly a far more elegant and sophisticated view of the genome than the historical ‘DNA®RNA®Protein’ paradigm, but it requires vastly more sophisticated tools and an open mind to decipher important regulatory elements amongst this backdrop of near universal transcription. Despite this complexity, early evidence from several studies, including our own, would appear document important regulatory functions for these longer, non-coding RNA species. Control of DNA imprinting, X-inactivation, DNA demethylation, gene transcription, and generation of other non-coding RNAs (e.g., microRNAs, small RNAs) have all been attributed to these medium and large RNA transcripts. Control of DNA imprinting, X-inactivation, DNA demethylation, gene transcription, and generation of other non-coding RNAs (e.g., microRNAs, small RNAs) have all been attributed to these medium and large RNA transcripts. (Costa 2007) In cancer, several novel ncRNAs have been identified and associated with breast and ovarian cancer. (Perez, Hoage et al. 2008) Interestingly, certain of these ncRNAs were found to be highly conserved, highly expressed, and consistently mutated in cancer when compared to the same patient’s normal DNA, exactly analogous to many cancer-associated protein-encoding genes like P53, strongly suggesting an important regulatory role potentially abolished by mutation in these cancers. In another study of hormonally refractory prostate cancer, 25 novel, non-conserved ncRNAs with small ORFs were identified arising from untranslated regions of unannotated RNA transcripts. (Quayle, Hare et al. 2007) More relevant to the present discussion, Chan et al. described a 1.25 kb non-coding, highly conserved RNA with at least 11 exons in rhabdomyosarcoma that is differentially expressed between the two major subtypes, alveolar (high expression) and embryonal (low expression). (Chan, Thorner et al. 2002) Interestingly, this ncRNA lies in close proximity to Myf5 and Myf6, important myogenic transcription factors in muscle and its malignant counterpart, rhabdomyosarcoma.

MYCN & MYCNOS Expression in Neuroblastoma

Fig 4: MYCN and MYCNOS (anti-sense MYCN) expression in neuroblasoma
In our own work, we find widespread evidence of important associations of ncRNAs with specific tumor types, as well as subtypes with differing prognoses. An example is shown in figure 5, where an unannotated RNA transcript, AK057037, is found to be the most significantly expressed RNA sequence in Ewing’s when compared to a wide variety of other childhood cancers. In silico modeling suggests this is a 2,641 base, 5 exon, non-coding gene with no orthologues in mouse, rat, zebrafish, C. elegans, or S. cerevisiae. It is exceedingly highly expressed only in Ewing’s when compared to rhabdomyosarcoma, osteosarcoma, Wilms’, and neuroblastoma (but is known to be expressed a moderate levels in breast, pancreas, and spleen). This is but one example of an abundance of such ncRNAs with highly statistically significant association with Ewing’s but not other tumors. Similar associations are readily found for other ncRNAs in other tumors when they are compared to a variety of other tumor types, as here.

**Summary**

Recent data conclusively show that RNA transcription is pervasive across nearly the entire genome. These non-coding RNA transcripts include several known (siRNA, miRs) and other largely unknown (TUFs, large ncRNA) non-coding, largely unannotated ‘genes’ with a strong statistical association with certain cancer types. This suggests they possess important regulatory functions in both normal development and cancer, and may be important diagnostic biomarkers as well as potential therapeutic targets.

**References**


New genetic insight into T-cell acute lymphoblastic leukemia

Over the last 20 years, numerous genetic abnormalities have been identified in T-cell acute lymphoblastic leukemia (T-ALL). Here, the current knowledge on these abnormalities will be reviewed, and a new classification for these aberrations is proposed into Type A abnormalities that may delineate specific T-ALL subgroups and Type B abnormalities that can be shared by several of these subgroups. Based on the pathogenic functions of several of these aberrations, new compounds have been proposed that may be used as new treatment modalities in future.

In contrast to childhood B-cell ALL for which the outcome has improved over the last decades to cure rates reaching nearly 85 percent, the outcome for children with T-ALL remains inferior. About 30 percent of the patients relapse within the first 2 years following initiation of current treatment protocols. As the overall survival rates in children now reaches ~70 percent, the outcome in adult patients is far worse with survival rates of only 30-40 percent.1

Until now, many different types of genetic abnormalities have been identified including various chromosomal translocations as consequence of erroneous TCR-rearrangements, non-TCR driven translocations, amplification, deletions and point mutations.2,3

Some of these abnormalities, which we denote as "Type A mutations", occur in a mutually exclusive fashion and are responsible to enforce an arrest at specific T-cell development stages (see Table). Based upon gene expression profiling studies using microarrays, growing evidence emerges that T-ALL may comprise at least 5 distinct subgroups each having unique gene expression signatures.4,6 Among these are the HOX11/TLX1 and HOX11L2/TLX3 subgroups comprising T-ALL cases with chromosomal translocations affecting the HOX11 or the HOX11L2 oncogenes, respectively. These 2 subgroups also separate 2 T-ALL entities that may have opposing prognostic relevance. HOX11-positive T-ALL has been associated with excellent prognosis,7,8 whereas HOX11L2 positive T-ALL in various studies has been associated with poor outcome.9,10

Other subgroups including the TAL/LMO and the HOXA subgroups may comprise various molecular-cytogenetic abnormalities affecting many different oncogenes. For instance, the TAL/LMO subgroup comprise T-ALL cases with chromosomal aberrations affecting one of the homologous basic helix-loop-helix genes (bHLH) TAL1, TAL2 or LYL1, and/or one of the homologous LIM-domain only (LMO) genes LMO1 or LMO2. As these bHLH and LMO genes encode for transcriptional cofactors that participate in a multifactor transcription complex and may therefore explain why these abnormalities result in an identical activation pattern of downstream target genes.3,6 Although the exact oncogenic role of this transcription complex has not been resolved, it may function by inhibiting the E2A/HEB transcription factors.11 As transcriptional repression requires recruitment of enzymes with histone deacetylase activity (HDAC), patients with TAL/LMO abnormalities may therefore benefit from combination treatment with HDAC inhibitors. The prognostic relevance for this subgroup is not yet clear.

The HOXA subgroup includes T-ALL cases with various different molecular-cytogenetic aberrations that are characterized by aberrant activation of various members of the HOXA gene cluster including HOXA9 and HOXA10.5,6,12

Among these abnormalities are rearrangements of the TCRß locus directly into the HOXA gene cluster due to an inversion on chromosome 7 (Inv(7)(p15q35))5,12 translocations resulting in CALM-AF10 or MLL fusion products,14 or a
deletion on chromosome 9 (del(9) (q34.11q34.13)) that results in a SET-NUP214 fusion product. The CALM-AF10, the MLL-fusion products, and the SET-NUP214 fusion products bind in the promoter regions of specific members of the HOXA gene cluster, and recruit the histone H3-Lysine79 methyltransferase hDOT1L that promotes further epigenetic chromatin modifications and HOXA genes activation. This subgroups may therefore benefit from histone H3-K79 methyltransferase inhibitors.

Cluster analysis of T-ALL patient samples based on the gene expression levels as assessed by microarrays further provided evidence for the existence of a fifth, immunophenotypic immature T-ALL subgroup. Thus far, no distinctive molecular-cytogenetic abnormality has been identified for this subgroup.

In contrast to Type A mutations, Type B mutations are present in T-ALL irrespective of the T-ALL subgrouping (see Table). Type B abnormalities therefore reflect common abnormalities and affect various cellular processes including cell cycle, T-cell commitment and selfrenewal, T-cell receptor (TCR) signaling processes, or result in the aberrant activation of tyrosine kinases.

In relation to loss of cell cycle regulators, the most important abnormalities observed in T-ALL are homo- or heterozygous deletions of the Cyclin/D Cyclin-Dependent Kinase-4 (CDK4) inhibitors p15/CDKN2B, p16/CDKN2A in about 65 percent of pediatric T-ALL cases. The CDKN2A locus also encodes for the alternative p14ARF gene, which is part of the p53-regulated cell cycle and apoptosis regulating machinery. This percentage may currently underestimate the true percentage of inactivation of these loci in T-ALL as silencing by especially promoter hypermethylation has been described which may provide a rational for DNA methyltransferase inhibitors. Also inactivation by point-mutations or post-transcriptional modifications has been described. Loss of p16 and/or ARF have been shown in mouse models to promote T-cell leukemogenesis, whereas reintroduction of these loci delayed oncogenesis.

The transmembrane receptor NOTCH1 is important during hematopoiesis and promotes self-renewal of the stem-cells compartment and promotes T-lineage commitment of early lymphoid progenitor cells. For long times, NOTCH1 has been implicated in T-ALL leukemogenesis due to its involvement in a rare translocation t(7;9). More recently, NOTCH1 appeared mutated in more than 50 percent of T-ALL cases. Mutations are located in the heterodimerization (HD) or adjacent juxtamembrane domains. Other mutations disrupt the C-terminal PEST-domain which normally functions as target for the F-box protein FBXW7 as part of the E3-ubiquitin ligase complex that targets ICN for proteolytic degradation. PEST mutations can occur in combination with HD-mutations. NOTCH1 mutations promote ligand-independent NOTCH1 cleavage by proteases including γ-secretase, resulting in the release of intracellular NOTCH1 (ICN) that functions as a transcription factor. Therefore treatment of T-ALL using γ-secretase inhibitors seemed promising. However, a phase I/II clinical study using γ-secretase inhibitors in children with T-ALL was thus far unsuccessful due to low anti-tumor effectiveness and severe gastro-intestinal toxicity.

The FBXW7 gene is also frequently inactivated by mutations in 8-30% of T-ALL patients, occasionally in combination with NOTCH1 HD mutations, and provides an alternative mechanism for NOTCH1 activation in T-ALL. The presence of NOTCH1 mutations and/or FBXW7 mutations have been related with good initial treatment response and good outcome. During normal T-cell development, NOTCH1 proved to be an important transcription factor that activated various genes. It also controls the assembly of the pre-TCR complex during T-cell development by regulating the expression of the preTCR alpha gene (pTα). For various T-ALL oncogenes, a pivotal synergistic role for this preTCR complex has been demonstrated for T-cell leukemogenesis. An important oncogenic role of this complex was further supported by the finding of rearrangements or (in)activating point mutations in direct downstream signaling components of this complex, or in the closely associated RAS-MAPK and the PI3K-AKT pathways.
Table 1: Frequency of molecular-cytogenetic aberrations in T-ALL, relation to outcome and potential therapeutic targets.

<table>
<thead>
<tr>
<th>Type A Rearrangement</th>
<th>Gene(s)</th>
<th>Outcome</th>
<th>Freq (%)</th>
<th>Therapeutic inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t(1;14)(p32;q11) ) / ( t(1;7)(p32;q34) )</td>
<td>TALI</td>
<td>Good?</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>1p32 deletion</td>
<td>TALI</td>
<td>Good?</td>
<td>4</td>
<td>HDAC inhibitor</td>
</tr>
<tr>
<td>( t(7;9)(q34;q32) )</td>
<td>( \text{SIL/TALI} )</td>
<td>Unknown</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>( t(11;14)(p15;q11) / ) ( t(7;11)(q34;p15) )</td>
<td>LMO1</td>
<td>Unknown</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>( t(11;14)(p13;q11) / ) ( t(7;11)(q34;p15) )</td>
<td>LMO2</td>
<td>Unknown</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>11p13 deletions</td>
<td>LMO2</td>
<td>Unknown</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HOX11</td>
<td>( t(10;14)(q24;q11) / ) ( t(7;10)(q34;p24) )</td>
<td>HOX11</td>
<td>Good</td>
<td>8</td>
</tr>
<tr>
<td>HOX11L2</td>
<td>( t(5;14)(q35;p32) )</td>
<td>HOX11L2</td>
<td>Poor</td>
<td>24</td>
</tr>
<tr>
<td>inv(7)(p15q34) / ( t(7;7)(p15;q34) )</td>
<td>HOXA</td>
<td>Undefined</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>( \text{CALM-AF10} ) ( \text{MLL-ENL} ) ( \text{SET-NUP214} ) ( \text{LYL1} )</td>
<td>Poor</td>
<td>Unknown</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>( t(7;19)(q34;p13) )</td>
<td>( \text{BHLHBI} ) ( \text{MYB} )</td>
<td>Unknown</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>( t(14;21)(q11.2;q22) ) ( t(6;7)(q23;q34) )</td>
<td>Unknown</td>
<td>Unknown</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type B Rearrangement</th>
<th>Gene(s)</th>
<th>Outcome</th>
<th>Freq (%)</th>
<th>Therapeutic inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{9p21 deletions} ) hypermethylation</td>
<td>( \text{CDKN2A/2B} )</td>
<td>Unknown</td>
<td>70</td>
<td>DNA methyltransferase</td>
</tr>
<tr>
<td>( t(7;12)(q34;p13) / ) ( t(12;14)(p13;q11) ) ( t(7;9)(q34;p34) )</td>
<td>( \text{CDKN2A/2B} ) ( \text{CCND2} ) ( \text{NOTCH1} )</td>
<td>Unknown</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>NOTCH1 Mutations</td>
<td>( \text{NOTCH1} )</td>
<td>Good</td>
<td>&gt;50</td>
<td>γ-secretase inhibitors</td>
</tr>
<tr>
<td>( t(1;7)(p34;q34) ) Mutations</td>
<td>( \text{FBXW7} ) ( \text{LCK} ) ( \text{RAS} )</td>
<td>Good</td>
<td>9-30</td>
<td>SRC kinase inh.</td>
</tr>
<tr>
<td>( \text{(pre) TCR} ) 17q11.2 deletion</td>
<td>( \text{NFI} ) ( \text{PTEN} )</td>
<td>Unknown</td>
<td>3</td>
<td>inhibitor</td>
</tr>
<tr>
<td>10q23.31 deletion Mutations</td>
<td>( \text{PTEN} )</td>
<td>Unknown</td>
<td>17</td>
<td>P13K/AKT inhibitors</td>
</tr>
<tr>
<td>differentiation</td>
<td>( \text{MYB} ) ( \text{NUP214-ABL1} ) ( \text{EML1-ABL1} ) ( \text{ETV6-ABL1} )</td>
<td>Unknown</td>
<td>8-15</td>
<td>ABL kinase inhibitor</td>
</tr>
<tr>
<td>tyrosine kinase</td>
<td>( \text{BCR-ABL1} ) ( \text{ETV6-JAK2} ) ( \text{FLT3} )</td>
<td>Unknown</td>
<td>&lt;1</td>
<td>3</td>
</tr>
</tbody>
</table>
pathways. These include aberrant expression of SRC-kinase LCK due to the t(1;7) translocation (<1%), activating RAS mutations (~8-10%), inactivating deletions/mutations of the RAS regulator NF1 (~3%), or inactivating mutations of PTEN (~17%) resulting in constitutive activation of the AKT survival pathway. This may also provide new therapeutic rationales to treat T-ALL with either SRC-kinase inhibitors, farnesyltransferase inhibitors or PI3K-AKT inhibitors.

A last category of mutations that will be reviewed involves the formation of fusion products with potent tyrosine kinase activity. Several of these fusion products affect the tyrosine kinase domain of ABL1 due to rare translocations including BCR-ABL1, EML1-ABL1 and ET6-VABL1. The NUP214-ABL1 fusion product due to an extra chromosomal amplification has been identified in ~6% of T-ALL cases. So far, this abnormality has predominantly been identified in T-ALL subclones of the HOX11L2, HOX11 and HOXA subgroups, suggesting that it represent an important mechanism for disease progression as a relative late event in T-ALL that synergizes with deregulated HOX genes. Activation of the tyrosine kinase activity of FLT3 due to tandem duplications in the juxtamembrane domain have been identified in leukemic subclones of less than 3% of the T-ALL cases. Although NUP214-ABL or mutant FLT3 positive T-ALL may respond to potent tyrosine kinase inhibitor, including Imitinib or PKC412, such treatment may only be effective to these leukemic subclones while leaving the residual T-ALL cells of the original clone unharmed.

For the next years to come, it will remain important to identify new chromosomal abnormalities in T-ALL. Especially in the light that still about 40 percent of all T-ALL cases, a characteristic Type A mutation needs to be identified. Identifying these hits, studying their function and their role in the activation of downstream target pathways and their mechanisms of synergy with other Type B mutations, may reveal new therapeutic options for this high-risk disease, but may also provide new insights in pathogenic mechanisms of other diseases.

References
Section B

New Horizons in Pediatric Oncology
(Practical Solutions for Overcoming Professional Myopia)

Robert J. Arceci

The title I was given for this discussion was “New Horizons in Pediatric Oncology.” Ironically, a horizon is something that can never be reached, but continues to change as one approaches it. While this may indeed be the case of curing the elusive and deadly cancers that afflict children and adolescents, our only response as clinical and laboratory investigators is to work with the goal of finding practical solutions that are indeed obtainable. Thus, this discussion will focus on what challenges we currently face. In addition, we will discuss how creative and cooperative investigators, caretakers and other key people can utilize novel technologies and strategies to solve these challenges.

Current Report Card

The initiation and expansion of the "war on cancer" in the United States began in the early 1970s with an infusion of government support that was essential to fuel the development of clinical co-operative groups, drug screening programs, specialty training, and comprehensive cancer centers with a focus on research, clinical trials and prevention. Efforts in other developed countries also contributed significantly to these developments. And from the beginning, pediatric oncology has been an important part of these efforts.

On the success side of this ledger is the commonly referred to achievement of pediatric oncology in increasing the overall cure rate of children with cancer to approximately 80% with decreases in mortality of about 2% per year over the past three decades. Work in pediatric cancers has been able to place first claims on the biological underpinnings of cancer with the development of the “two hit” hypothesis as well as the identification of the retinoblastoma gene, Rb, as the first tumor suppressor gene. Such discoveries have had a broad impact on clinical and laboratory investigators in both pediatric and medical oncology.

A far greater percentage of children compared to adults are enrolled on experimental clinical trials. Pediatric oncology care is nearly always multidisciplinary in its planning and execution, thus increasing the critically important integration and timing of surgical, radiotherapy and chemotherapy aspects of care. In addition, pediatric oncology has been a pioneer in developing rigorous, pre-emptive supportive care to reduce morbidity and mortality. There has also been an enormous amount of effective creativity in optimally using old drugs in new ways, because very few new drugs have been developed with specific indications first in pediatric cancers. In this regard, the use of “older drugs” along with the standardized approaches to care have made the cost associated with curing children with cancer quite a bargain, especially when considered in terms of cost per life years saved. Furthermore, as a result of these successes and children surviving their original cancers, pediatric oncology has been instrumental in identifying adverse late effects and survivorship issues. On the other side of this coin is the pioneering work that has been done in terms of palliative care and psychosocial support for children with cancer and their families.

There are also areas in which our report card may claim less success. We still have not determined in detail the cause and sequence of molecular events leading to or characterizing childhood cancers, including interactions with environmental and host risk factors. We have been slow in definitively testing novel approaches to care and incorporating them into standard therapy regimens leading to the reduction of conventional chemotherapy and radiation exposures. While some exceptions certainly exist, such as in Hodgkin lymphoma,
risk stratified care in leukemia and central nervous system tumors, there are major areas in which much more progress is needed.

In developed countries, cancer remains the major cause of disease related death in children and second only to accidents as an overall cause of death. Thus, a significant percentage of children are still not cured of their cancer, and in those who are cured, there are considerable short and long term adverse sequelae to face. The cure rate has also shown signs of decreasing. There has furthermore been the identification of underserved groups, such as adolescents in all settings as well as children of all ages in developing countries. The success of some of the “twinning programs” has been laudatory but represents just a beginning. We have not been able to effect comprehensive health care coverage for pediatric patients with cancers or the survivors of their childhood cancers. We have done little in the way of prevention, which may tie into the issue of improving our understanding of the causes of childhood cancer.

Thus, we have had excellent grades in several specific areas but average to failing grades in other areas. To successfully finish the goal of eradicating the burden of cancer in children and adolescents, and of course in patients of all ages, that was started in earnest over three decades ago, we need to look to the future with a renewed co-operative and expanded resolve.

How to finish the job

The first principles for achieving the eradication of the burden of cancer include believing that it can be done, freeing ourselves from reliance on non-paradigm shifting concepts and working globally with all stakeholders. Of course, the stakeholders represent essentially everyone, as we are all at risk of fate handing us such a diagnosis. Let’s examine some specific issues.

A critical challenge in pediatric oncology is how to identify and cure children with very high risk cancers. Some examples include the approximately 20% of patients with ALL who have refractory disease, many subtypes of AML, advanced staged sarcomas, neuroblastoma, Wilms tumor with diffuse anaplasia, high grade gliomas and aggressive brain tumors in the very young. Giving first priority to this challenge is not meant to undermine the need for efforts to develop less toxic therapies for all patients. However, patients with high risk cancers have a poor outcome regardless of the therapeutic approaches used. Thus, there must be an increasing emphasis on improving our understanding of the biology of these disorders, including their mechanisms of resistance as well as the critical survival pathways upon which they depend. Technological approaches to generate detailed and comprehensive molecular changes that define physiological behavior of the bulk as well as the tumor-initiating stem cells in such cancers are essential. Such technologies are nearly all currently available, although more robust bioinformatic approaches are being developed to integrate such complex datasets into predictive models of cell behavior and response to therapies. This type of biology does not come cheaply. A comprehensive, integrated and adequately supported approach is needed. This may indeed require decreasing the credit given to individuals while recognizing the successes of a group. While this concept has been discussed by academic leaders, it has not been practically embraced by universities. In many ways, pharmaceutical companies have mastered this approach to discovery and application much more so than academia.

There also needs to be bold, paradigm-shifting approaches to the translation of new knowledge into clinical trials for high risk patients. This point leads to another significant challenge for the future, i.e., how to perform informative clinical trials in distinct groups of patients with tumors with extensive heterogeneity. Advances in molecular and genetic medicine have revealed that the genetic make-up of patients from different racial backgrounds, of different gender, of different ages and of varied socioeconomic circumstances can have profound effects on outcomes. The differences in some instances are due to variations in the absorption and metabolism of drugs. The problems of obesity and malnutrition and their impact on cancer etiology and outcomes need to also be carefully studied.

An important consequence of such detailed delineation of different types of cancer and of patients is the recognition of the extraordinary
heterogeneity that exists. One logical conclusion to be made from such information is that future clinical trials could have cohorts with an N of 1. Obviously, this would undermine the ability to perform informative clinical trials for determining efficacy of a new treatment. Alternative approaches will therefore need to be carefully considered. Certainly, one aspect of a solution will be the increasing dependence on international trials balanced by the identification and targeting of critical genetic or molecular pathways that are shared by groups of patients.

There are, of course, many regulatory hand-cuffs that currently slow down and prevent the development, performance and reporting of clinical trials. These regulatory impediments are local, regional, national and international. They involve exchanging tissue specimens and data as well as the cost of clinical care and trial participation, differences in informed consent as well as data collection and reporting standards. However, none of these regulatory issues are absolute or unchangeable. After all, one must first realize that we or our representatives are their originators. While some things in the universe may be more immutable, certainly rules that are created by men and women should be changeable for the benefit of men and women.

An alternative approach that could also aid in drug testing is development of more predictive pre-clinical models. This point brings up an enormous challenge in developing more effective therapies. Randomized clinical trials in pediatric oncology have shown that, over the past several decades, investigators have not been able to consistently predict whether a new therapy will result in an improved outcome. For instance, over the past 40 years, the introduction of new therapies has resulted in improvements (often with increased toxicity), in about 50% of randomized trials. While this inability to predict outcome in such trials leads to ethical equipoise, and thus, an acceptable and comfortable paradigm for clinical investigators, a less optimistic view might be that we are quite poor in predicting which new therapies will work.

Can truly predictive pre-clinical models involving animal models or, possibly, computer generated molecular models of patient and cancer, be developed? There are notable examples of animal models that have been useful, particularly, in the hematopoietic malignancies. Overall, however, there are few truly representative and accurately predictive pre-clinical animal models. Unfortunately, human beings and the tumors which they get are simply not as uniform as those generated in animal models.

More representative and predictive animal models should be generated with a rigorous characterization of various human cancers as well as the acknowledgement that genetically homogenous host animals and tumors resulting from introduced alterations in one or two molecular pathways are unlikely to be optimal approaches. However, it is presently unclear how to build models with underlying genetic and epigenetic heterogeneity and instability, two fundamentally important characteristics of human cancers. In this regard, one might consider the utility of xenograft models. Unfortunately, they also have significant limitations in their ability to maintain representative genotypes, gene expression patterns and phenotypes. How we utilize the tools of molecular medicine to improve our understanding of cancer and the patients who develop it will greatly impact on whether we turn this opportunity into a success leading to improved patient outcomes. To this end, one should be able to envision the eventual development of computer models that encompass all the host and tumor critical characteristics such that the most effective therapy can be initiated and the response predicted from a rapid in silico modeling program.

The issue of the quality of survivorship for many children and adolescents with cancer is also a critical challenge. The results from a recent study of over 10,000 childhood cancer survivors demonstrated a significantly increased risk of having chronic health care problems as well as shortened life-spans compared to their siblings. The patients in the Oeffinger et al. study were diagnosed before 1976. The suggestion has been made from such data that the problems of the past have not been subsequently repeated and that future generations of survivors will enjoy improved health, psychosocial and societal opportunities. There is, of course, no guarantee
that this will be the case. The 1980s and 1990s have often been characterized as the decades of dose intensification, suggesting that there may still be significant adverse long-term sequelae awaiting this group of survivors. In either case, there remains a growing need to understand the genetic predisposing factors leading to increased responsiveness to chemotherapy as well as short and long-term toxicities. Understanding genetic, predisposing factors leading to increased responsiveness to chemotherapy as well as short and long-term toxicities will be essential to developing effective, alternative strategies.

The best way to prevent adverse long-term sequelae from cancer and/or its treatment is to prevent the development of cancer. While prevention efforts have become increasingly important in a wide variety of cancers in adults, such as those of the colon, lung and breast, the concept of prevention for pediatric cancers has been usually viewed unenthusiastically or as, at best, unrealistic. However, success with vaccination programs such as those against papilloma virus and its link to cervical cancer or hepatitis B and liver cancers should provide renewed hope for such approaches. 14-16 Pediatrics has often led the way in terms of the prevention of a wide variety of devastating infections through vaccination programs. It would seem that there is yet an opportunity to extend such approaches to the prevention of common forms of leukemia and other childhood cancers. This is especially relevant when one considers some of the new concepts concerning the existence of pre-malignant, precursor cells as a potential, interventional target. One must be able to dream of the day when infants will receive vaccinations against DPT, polio, Varicella and ALL.

While these biological and clinical challenges are immense, they unfortunately do not compare in magnitude with the challenge of eradicating health care disparities and access to care for all children (and all patients) with cancer and other catastrophic diseases. This is an issue for local, state, national and global action. The means to provide such care is within the reach of our civilization and should be an issue around which people from all backgrounds can work together to implement solutions.

Some parting shots

Addressing challenges as immense as these will take comparable levels of imagination, focus and support. Resources currently allotted for purpose, remain insufficient. Inadequate funding of science and health care short changes current and future generations, while being a particularly poor business strategy. There should be a "global comprehensive cancer center" that integrates some of the scientific and clinical solutions discussed above. There seems to be no real advantage for having unnecessary regulations that differ among institutions, regions and countries when the goals are identical. There are times when I wonder whether the system we have was the brainchild of the galactic beaurocrats, the Vogons, from Douglas Adams' Hitch Hikers's Guide to the Galaxy who would rather develop and discuss rules and regulations rather than real solutions. 17 But alas, we are those Vogons, i.e., we and the people in our institutions as well as those who represent us in government. There should be a global cry of dissatisfaction with such a status quo that in turn is translated into an action plan at all levels of engagement.

As part of such a "global comprehensive cancer center" one could build on some of the successes of international trials and expand the utility of internet posting of protocols that are straightforward, including consents, data collection and reporting. All of this can be done electronically through internet computer or cell phone technology from nearly anywhere. Similarly, reminders of data to be collected, etc., could be linked through internet and cell phone technologies, similar to that being pioneered for malarial prophylaxis by Nokia. Systems exist to assure the integrity and confidentiality of data. There simply should be no acceptance of consent forms that read like encyclopedias or legal histories. There seems to be little reason why a child's privacy and well-being should be handled differently in the USA compared to other countries. I would propose that the major pediatric cooperative groups and organizations begin such a process in earnest with the establishment of a structure and task forces to come up with practical plans and timelines for the major areas of work.

The expansion of the "twinning programs"
approach is likely to continue to make a positive impact for children with cancer in developing countries. Standard approaches to diagnosis, clinical trials and reporting of data and outcomes as noted above would also benefit such programs by minimizing the need to re-invent such programmatic parts with each initiative. Such programs can also help to establish and provide standards of culturally sensitive treatment, survivorship and palliative care.

Advocacy efforts need to be broadened to take on more global goals and organization. Such efforts should also possibly be linked to the care of children with other serious diseases not only cancer. While support would ideally be channeled locally, there is also an opportunity for some of the wealthier countries and organizations helping to support less wealthy programs as is already being pioneered by several groups.

The integration of currently available and developing technologies with organizational changes and renewed resources should provide both more effective and less toxic curative therapies to be tested and then incorporated into standards of care. The beneficiaries of these efforts will be children with cancer and their families in developed and in developing countries. I would propose that the major pediatric cooperative groups and organizations begin such a process in earnest with the establishment of a structure and task forces to come up with practical plans and timelines for the major areas.

Mark Twain stated that "Twenty years from now you will be more disappointed by the things that you didn't do than by the ones you did do." We should not look with regret and disappointment for the things we didn't do, but instead, be galvanized and unified by what can be accomplished. More than ever, the fight to cure children with cancer represents an archetype of the problems and challenges all people with cancer and other devastating diseases. We have been out in front of the fight before. There is no reason not to be leading again.

References