Paediatric Oncology - The Past and the Future

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2008 marks the 40th anniversary of the founding of the Societe Internationale Oncologie Pediatriche 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 e.g. 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 e.g. 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 sub continent 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 become 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 work in the more economically advanced 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 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 new 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.