Risk-based Treatment for Children with Neuroblastoma

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Neuroblastoma Tumors are Heterogeneous

The clinical hallmark of NB is heterogeneity, with the likelihood of tumor progression varying widely according to age at diagnosis, the stage of disease, and tumor biology [1,2]. Numerous transformation-linked genetic and epigenetic changes have been identified that have contributed to the understanding of neuroblastoma tumor biology, and many of these tumor-specific genetic and epigenetic aberrations are highly predictive of treatment response and outcome [1,3,4]. Because of the heterogenous behavior of neuroblastoma tumors, modern treatment strategies are stratified according to patient risk, defined by both clinical and biological factors. Numerous studies have validated the concept of risk group-directed therapy and the usefulness of biological prognostic variables. However, at the present time, the risk-grouping systems used in North America, Europe, Japan, and Australia are not uniform. It is, therefore, difficult to directly compare the results of clinical trials conducted in different regions. To address this problem, efforts to develop a uniform International Risk Group (INRG) classification system are ongoing. Below we have outlined the criteria that are currently used to define risk group and stratify treatment within COG and the European SIOP Neuroblastoma Group (ESIOP NB).

Patient Age and Stage

As with most malignancies, stage of disease is a significant prognostic factor in NB [5]. Over the past two decades, several different staging systems have been used to classify extent of disease. The Evans staging system [6] is based on clinical criteria, whereas both the Paediatric Oncology Group (POG) [7] and the tumor-node-metastasis (TMN) classifications [8] are surgicopathologic systems. In an effort to develop a uniform staging system based on both clinical and surgicopathologic findings, the INSS was developed by an international consensus group [9,10]. Retrospective analyses have confirmed that the INSS criteria identify prognostic subsets of patients with NB [11,12], and the INSS has now been implemented world wide.

Age at diagnosis remains the only other independent clinical prognostic factor. For all stages of disease beyond localized tumors, infants less than 1 year of age have significantly better disease-free survival than older children with equivalent stages of disease.[6,13] The currently accepted age cut-off of 365 days was based on the observations made by Breslow and McCann over 30 years ago [13]. Although their results suggested that days of age should be used for risk stratification as a continuous variable, this is not clinically practical. Instead, age has been used as a prognostic variable with the convenient cut-off of 365 days. More recent studies suggest that 365 days may not be optimal age to discriminate risk. Look and co-workers reported that 1- to 2-year old children with disseminated disease have a better outcome than children over 2 years of age [14]. Two additional studies have demonstrated excellent outcome in a subset of toddlers (12-18 months of age) with stage 4 disease who were treated with multi-agent chemotherapy [15,16].

In an effort to identify the statistically optimal age cut-off, London and co-workers recently analyzed the influence of age on outcome in 3,666 patients treated on CCG and POG studies [17]. These studies confirmed that the prognostic contribution of age to outcome in neuroblastoma is continuous in nature. Although no clear delineation of an age cut-off was detected, strong statistical evidence was found for an age cut-off between 15-19 months. Further analyses of a larger, international cohort of patients are ongoing. Based on these studies, it is anticipated that a new age cut-off for risk-group assignment will incorporated into the INRG.

MYCN Amplification

MYCN amplification occurs in approximately 20% of primary NB tumors and is strongly associated with the presence of metastatic disease and poor prognosis [18]. These observations suggest that *MYCN* critically contributes to the clinically aggressive behavior of high-risk NB tumors, and a number of laboratory studies support this hypothesis. The level of expression of *MYCN* has been shown to directly correlate with growth potential of NB cells [19,20]. More recent studies have shown that *in vivo* tumor growth can be inhibited with *MYCN* anti-sense oligomers [21]. Transgenic mice with targeted expression of *MYCN* have provided further evidence of the critical role *MYCN* plays in NB pathogenesis [22].

COG Risk-Group Classification System and Treatment Stratification

In addition to age (< vs > 1 year), INSS stage, and tumor *MYCN* status, the current COG Risk Classification System also includes tumor histology and ploidy. Treatment is stratified according to risk-group assignment as indicated in the Table below.

The overall objective of the recently closed COG low-risk study (P9641) was to preserve the excellent survival rate for patients with low-risk NB by using surgery as the primary treatment approach, thereby minimizing the risks of acute and long-term chemotherapy-related morbidity for the majority of these patients. Based on the excellent outcome and high rate of spontaneous remission of localized tumors that has been reported in the mass screening studies [23], the COG has also recently developed a clinical trial in which infants with small adrenal primary NBs will be observed rather than undergo major surgery (ANBL00P2).

Excellent survival rates have also been observed for patients with intermediate-risk disease following treatment with chemotherapy and surgery [24,25]. However, the use of adjuvant therapy for patients with regional disease has been challenged in a single institution study in which a subset of patients with INSS stages 2B and 3 tumors that lacked *MYCN*-amplification survived without disease progression following surgery alone [26]. These observations suggest that for the majority of patients with biologically favorable regional tumors, chemotherapy may

Table : COG Risk-Group Classification System

INSS Stage	Age	*MYCN* Status	Shimada	DNA Index	Risk Group
1	0-21 y	Any	Any	Any	Low
2A/2B	< 365 days	Any	Any	Any	Low
	> 365 days-21 years	Normal	Any	–	Low
	> 365 days-21 years	Amplified	Favorable	–	Low
	> 365 days-21 years	Amplified	Unfavorable	–	High
3	< 365 days	Normal	Any	Any	Intermediate
	< 365 days	Amplified	Any	Any	High
	> 365 days-21 years	Normal	Favorable	–	Intermediate
	> 365 days-21 years	Normal	Unfavorable	–	High
	> 365 days-21 years	Amplified	Any	–	High
4	< 365 days	Normal	Any	Any	Intermediate
	< 365 days	Amplified	Any	–	High
	> 365 days-21 years	Any	Any	–	High
4S	< 365 days	Normal	Favorable	> 1	Low
	< 365 days	Normal	Any	= 1	Intermediate
	< 365 days	Normal	Unfavorable	Any	High
	< 365 days	Amplified	Any	Any	High

be safely reduced or eliminated. In an effort to avoid associated acute and long-term complications while maintaining high cure rates, adjuvant chemotherapy and radiotherapy have been reduced in the current COG Intermediate-Risk Study (A3961). Intermediate-risk patients with favorable biology tumors are treated with a short course of chemotherapy (4 cycles), while intermediate-risk patients with unfavorable biology receive a longer course of chemotherapy (8 cycles).

Unfortunately, outcome remains poor for children with high-risk disease. During the past decade there has been only a modest improvement in survival, which is thought to be due to intensification of induction chemotherapy, megatherapy consolidation, and improved supportive care. Several clinical trials, including the large prospective randomized CCG-3891 study which demonstrated superior outcome for patients randomized to myeloablative therapy and bone marrow transplant versus chemotherapy during consolidation [27], support the hypothesis that dose intensification is an important component of successful treatment of NB [28]. The differentiation agent 13-cis retinoic acid was shown to be clinically effective when administered in the setting of minimal residual disease in the randomized CCG 3891 clinical trial [27]. This seminal study demonstrated that a biologic agent was capable of impacting outcome in high-risk NB.

The COG is currently conducting a study that includes 6 cycles of intensive induction chemotherapy and surgery, followed by myeloablative chemotherapy with PBSC rescue and local radiation (A3973). Patients are randomized prospectively to receive purged PBSCs versus non-purged PBSCs. Patients who achieve a VGPR/CR are then eligible for a second randomized study testing the efficacy of Ch14:18 anti-GD2 antibody plus cytokines in combination with 13-cis retinoic acid to 13-cis retinoic acid alone in the setting of minimal residual disease. It is anticipated that this study will be closed in accrual in the Spring of 2006.

ESIOP NB Risk-Group Classification System and Treatment Stratification

The European SIOP Neuroblastoma Group (ESIOP NB) was founded in 1994. Its first study (LNESG 1), which was activated on January 1995, was designed for patients with localized disease (approximately half of all NB patients). Three subgroups were defined based on the extent of the initial surgical approach (complete tumor resection, resection with minimal residue, resection with gross residue or biopsy only). In an effort to define common criteria for tumor operability, surgical risk factors (SRF) were identified based on the radiological characteristics of the tumor. In presence of any SRF, the surgeon was encouraged to limit the primary operation to a biopsy and perform a second surgery following chemotherapy. As a consequence, some patients who would previously have been considered operable were entitled to receive neo-adjuvant chemotherapy and were defined stage 2 unresectable (2U). Preliminary results of the study indicate that patients who underwent surgery in presence of SRF had lower chance of having a complete tumor resection and had a greater risk of developing surgery-related complications.

LNESG 1 included a trial for patients with stage 2 disease without *MYCN* gene amplification for whom no adjuvant therapy was to be given. Of 124 evaluable patients with a median follow up of 62 months, OS at 5-year is 93.0% and RFS is 83.0%.[29] The occurrence of relapse was greater in presence of unfavorable histology (INPC categories[30]) and high LDH level.

A second study (INES Study), which was designed for infants with NB, opened in 1999. It included four trials:

- 99.1 was developed for infants with unresectable disease. These patients received low-dose chemotherapy (Vincristine plus Cytoxan, or Carboplatin plus Etoposide in case of symptomatic spinal cord compression, or other relevant symptoms);
- 99.2 was developed for infants with stage 4s (independently of primary tumor extension). These patients were observed if the Philadelphia score was under 2 for infants greater than 1 month of age or if the score was 1 for younger age infants. Patients with stage 4 disease without bone, lung, or CNS metastases were also eligible for this trial in the absence of relevant clinical symptoms. Bone disease was defined as positive skeletal

mIBG uptake with abnormal X-ray and/or CT findings

- 99.3 was designed for patients with stage 4 with bone disease (positive skeletal mIBG uptake associated with radiological or CT abnormalities), or metastases to lung, or CNS;
- 99.4 was developed for patients with stage 2, 3, 4 and 4s with documented *MYCN* gene amplification in tumor cells.

The four trials were closed to patient registration in June, 2004. Preliminary results after a median follow-up of two years are as follows:

99.1 of 110 evaluable patients, 10 relapsed (8 local, 2 metastatic) after a median of 16 months from diagnosis. OS and EFS are respectively 100% and 91%

99.2 of 104 evaluable patients, 52 did not receive any chemotherapy. There were two disease-related deaths with OS 97.3% and EFS 89.6%

99.3 of 48 evaluable patients, 4 relapsed with one subsequent disease-related death. OS and EFS are 97.7% and 85.9%, respectively

99.4 of 42 evaluable patients, none died of toxicity. Thirty % of patients did not respond or experience disease progression during treatment. Only 14 underwent megatherapy. Overall results were poor (OS and EFS 36%), and were worse for patients with stage 4 compared to other stages.

In February 2002, ESIOP NB activated a Protocol for high-risk patients including stage 4 above 1 year and stage 2 and 3 with amplified *MYCN* gene. The therapeutic scheme included induction therapy with COJEC regimen (8 cycles given at 10-days intervals), followed by high-dose chemotherapy (randomization between CEM and BuMel) in case of response, irradiation of primary tumor site and oral retinoic acid. The protocol is on-going and has recruited approximately 500 patients so far.

The ESIOP NB Risk-Group Classification System is shown in the Table below. Similar to COG, treatment is stratified according to risk-group assignment.

Table 2 : ESIOP NB Risk Group classification

ESIOP Stage	Age	*MYCN* Status	Risk Group	Protocol	Chemotherapy
1	0-18 y	Any	Low	LNESG 2	None
2R & 3R	0-11 m	Normal	Low	LNESG 2	None
	0-11 m	Amplified	High	99.4	Intensive
	>12 m – 18 y	Normal	Low	LNESG 2	None
	>12 m – 18 y	Amplified	High	HR-NBL-1	Very intensive
2 U & 3 U	0-11 m	Normal	Intermediate	99.1	Low-dose
	0-11 m	Amplified	High	99.4	Intensive
	>12 m – 18 y	Normal	Intermediate	Unresectable	Low-dose
	>12 m – 18 y	Amplified	High	HR-NBL-1	Very intensive
4	0-11 m s bone mets ^	Normal	Low	99.2	None*
	0-11 m c bone mets	Normal	Intermediate	99.3	Low-dose
	0-11 m	Amplified	High	99.4	Intensive
	>12 m – 18 y	Any	High	HR-NBL-1	Very intensive
4S	0-11 m	Normal	Low	99.3	None*
	0-11 m	Amplified	High	99.4	Intensive

R, resectable; U, unresectable; s=without; c=with

^ Bone metastases are defined as mIBG positive spots associated with abnormal X-ray and/or CT findings.

** in absence of life-threatening symptoms*

Future Directions

Although substantial progress has been made in the treatment of children with low- and intermediate-risk NB, cure rates for high-risk patients remain low. Additional dose-escalation of therapy for high-risk patients is likely to be prohibitive. Furthermore, despite this aggressive treatment approach, more than 50% of children with high-risk disease will relapse due to drug-resistant residual disease. Eradication of refractory microscopic disease remains one of the most significant challenges in the treatment of high-risk NB. Phase I and II studies testing new targeted therapies are being conducted throughout the world, and preliminary results suggest that targeted radiotherapy, immunotherapeutic molecules, new retinoids, anti-angiogenic agents, and other experimental therapeutics have activity against refractory disease. A number of studies integrating biologically-based treatment approaches with cytotoxic treatment are ongoing or in various phases of development. Hopefully, this approach will lead to improved survival for children with high-risk NB.

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