ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Advances in the Treatment of Neuroblastoma

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H&O What is the treatment landscape in neuroblastoma at present?

SC Recently, significant advances have been made in the treatment of children with neuroblastoma. The clinical behavior of neuroblastoma, which is a common pediatric cancer, can be predicted by a number of factors, including the patient's age at the time of diagnosis, the stage of disease, and the biologic features of the tumor. Using these clinical and biologic prognostic criteria, patients can be classified as low-, intermediate-, or high-risk, and treatment is then tailored accordingly. Patients with low- and intermediate-risk neuroblastoma are usually cured with surgery alone or surgery combined with modest doses of chemotherapy. In contrast, high-risk patients have tumors that are clinically more aggressive and more difficult to cure. During the last 10 years, the Children's Oncology Group (COG) has conducted clinical trials that have demonstrated that for patients with low- and intermediate-risk neuroblastoma, high survival rates are maintained with a reduction of therapy. The reduced therapy is associated with fewer treatment-related toxicities, leading to better long-term outcome for these children.

Progress has also been made in the treatment of children with high-risk neuroblastoma. Previous cooperative group studies conducted in North America and Europe have shown that intensifying treatment with high-dose chemotherapy and stem cell rescue improves the outcome of these children. In addition, in a recently completed randomized COG study, immunotherapy plus retinoic acid administered following consolidation was shown to significantly improve outcome compared to retinoic acid alone. The demonstration of the effectiveness of immunotherapy plus retinoic acid in the setting of minimal disease is a significant advance, and the results of this study were recently published in the *New England Journal of Medicine*.

H&O What challenges are seen with neuroblastoma treatment?

SC Although progress has been made, approximately 50–60% of high-risk patients are not cured with our current treatment, and many of those who do survive suffer significant toxicities related to the intensive treatment they have received. Children who are successfully treated with our current strategies pay a big price, as many of them have significant complications related to the treatment they received. The very high doses of therapy can affect growth and development, hearing and speech, cognitive abilities, and organ dysfunction. These children are also at increased risk for developing second cancers. Thus, our goal is to develop more effective therapies with less toxicity. To achieve this goal,

Table 1. International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification Schema

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	<18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	<18			NA		Hyperdiploid	F Low
	<12			NA		Diploid	I Intermediate
	12 to <18			NA		Diploid	J Intermediate
	<18			Amp			O High
	≥18						P High
MS	<18			NA	No		C Very low
					Yes		Q High
				Amp			R High

Amp=amplified; GN=ganglioneuroma; GNB=ganglioneuroblastoma; NA=not amplified.

L1=localized tumor confined to 1 body compartment and with absence of image-defined risk factors (IDRFs); L2=locoregional tumor with presence of 1 or more IDRFs; M=distant metastatic disease (except stage MS); MS=metastatic disease confined to skin, liver and/or bone marrow in children <18 months of age.

significant efforts to identify biologic targets that are druggable are ongoing, in an effort to personalize treatment for these children.

H&O Can you discuss any ongoing studies in neuroblastoma?

SC The COG-ANBL0531 (Phase III Study of Response- and Biology-Based Combination Chemotherapy and Surgery With or Without Isotretinoin in Young Patients With Intermediate-Risk Neuroblastoma) study just closed. This was a protocol for patients with intermediate-risk disease. The objective of this study was to further reduce the amount of chemotherapy administered, while maintaining a 3-year overall survival rate of 95% or higher.

There is also an ongoing high-risk study, ANBL0532 (A Phase III Randomized Trial of Single versus Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma), that is testing a new induction chemotherapy regimen. This trial was designed to investigate if intensifying consolidation with tandem cycles of high-dose therapy and stem cell rescue will lead to improved outcome.

H&O Are there plans to study immunotherapy in a frontline setting?

SC We have used immunotherapy in newly diagnosed patients, and our current data suggest that immunotherapy works best in the setting of minimal residual disease. Immunotherapy alone is not effective in patients

with bulky tumors, but studies combining chemotherapy and immunotherapy are ongoing. We are also testing the efficacy of a fusion humanized anti-GD2-IL 2 antibody in a phase II COG study.

H&O What is the International Neuroblastoma Risk Group classification system?

SC Although modern treatment is stratified according to risk around the globe, the criteria that have been used to define risk differ in various parts of the world, making it difficult to directly compare the results of clinical trials. To develop a uniform classification system, an international task force was established in 2005. This task force analyzed data from more than 8,800 patients, and identified 7 highly prognostic factors that have been used to define very low-, low-, intermediate-, and high-risk patients. This classification system is now being adopted by cooperative groups around the world. The ability to use homogenous definitions to classify patients into risk-groups will significantly enhance our ability to compare the results of clinical trials conducted by various cooperative groups.

H&O What are some of the criteria that are used to determine risk groups?

SC The International Neuroblastoma Risk Group Classification System was published in the *Journal of Clinical Oncology* in 2009. The criteria that are used to define risk include: age, stage, histologic features of the tumor, and tumor genetic markers (the status of the *MYCN* oncogene and chromosome 11q). Based on the combination of 7 prognostic markers, patients are categorized as very-low–, low-, intermediate-, or high-risk, and treatment is then stratified according to risk-group assignment.

H&O Where do research efforts need to focus?

SC While our current approaches have led to long-term survival for approximately 40% of high-risk patients, we currently do not have the tools to distinguish those patients who will respond to current therapies from those who are destined to fail. Thus, we need to further refine risk at the time of diagnosis so that we can offer alternative therapy for those patients who will not be cured. We also need to develop more effective, less toxic therapies for patients with high-risk neuroblastoma. Additional research, focused on targeting the specific pathways that drive clinically aggressive tumor growth, will bring us closer to our goal of developing effective, personalized treatment strategies.

Suggested Readings

National Cancer Institute. Phase III study of response- and biology-based combination chemotherapy and surgery with or without isotretinoin in young patients with intermediate-risk neuroblastoma. http://www.cancer.gov/clinicaltrials/search/view?cdrid=554708&version=healthprofessional.

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