Targeting the Right Treatments for Neuroblastoma

By Nancy J. Nelson

Like most childhood cancers, neuroblastoma is relatively rare. But it is the most commonly diagnosed cancer in the first year of life, and more than half of children diagnosed develop aggressive forms of the disease that are difficult to cure.

"Not only are there a lot of deaths in the high-risk population, but high-risk patients require very, very intensive therapy to cure them," said Darrell Yamashiro, M.D., Ph.D., professor of pediatrics and pathology at the Columbia University Medical Center in New York. "These treatments include autologous bone marrow and stem cell transplant, so the morbidity associated with these is significant as well."

Most of today's research focuses on improving the survival of these high-risk children. With more than 100 trials actively recruiting patients, most for relapsed or unresponsive patients, researchers are testing a broad range of treatments. Among them are various kinase inhibitors, vaccines, and methods of stimulating the immune system, as well as new combinations of standard chemotherapies and radiation.

"It's an exciting time for clinical scientists but also a challenging time for physicians and parents," said Peter Zage, M.D., Ph.D., assistant professor in the department of pediatrics at Baylor College of Medicine in Houston. "There is a wide range of new drugs and treatment strategies available for children with neuroblastoma."

Characteristics of Neuroblastoma

Neuroblastoma is a cancer of specialized nerve cells, called neural crest cells. The neural crest is part of the developing sympathetic nervous system that controls the functions of many organs such as the heart, stomach, intestines, lung, liver, and kidneys. Tumors are usually found in the neck, chest, abdomen, or pelvis. Neuroblastoma is a disease of early childhood, with two-thirds of cases developing before the age of 5 years.

One hallmark of neuroblastoma is its heterogeneity, in both where and how the cancer develops. Two-thirds of the roughly 700 new diagnoses each year in the U.S. develop in the abdomen, with half of those occurring in the adrenal glands, the small glands that sit on top of the kidneys.

"The clinical presentation is highly variable, ranging from a mass that causes no symptoms to a primary tumor that causes critical illness as a result of local invasion, widely disseminated disease, or both," according to John M. Maris, M.D., of the Center for Childhood Cancer Research at Children's Hospital of Philadelphia in his 2010 *New England Journal of Medicine* review.

While low and intermediate risk children have 5-year survival rates of more than 90%, 50%–60% of children with high-risk disease relapse, and the 5-year survival rate of those children is 40%–50%.

"There are a number of factors that dictate whether a tumor will behave aggressively or respond well to therapy and be highly curable," said Susan L. Cohn, M.D., professor and director of pediatric clinical sciences at the University of Chicago. Cohn and other researchers from around the world developed the International Neuroblastoma Risk Group Classification System by using data from 8,800 neuroblastoma patients from North America, Australia, Europe, and Japan. They proposed four categories of risk—very low, low, intermediate and high—on the basis of patients' age at diagnosis, tumor stage, histology and grade, DNA copy number, status of chromosome 11q, and MYCN amplification status. For example, younger age and whole-chromosomal gains are associated with more benign tumors, whereas deletions of chromosomes and amplification of the MYCN gene are predictive of more aggressive tumors.

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Homing In on Aggressive Tumors

Many researchers are trying to improve the treatment situation for those high-risk children. Low- and intermediate-risk patients undergo a range of standard therapies that includes watchful waiting, surgery, and chemotherapy. High-risk children undergo an intense regimen of chemotherapy, surgery, and myeloablative chemotherapy to kill cells in the bone marrow, followed by a bone marrow or stem cell transplant to rebuild the marrow and then radiation treatment. 13-*cis* retinoic acid was added to the treatment protocol in 1999, and the most recent addition, immunotherapy, consists of a monoclonal antibody to a ganglioside, GD2, found on the surface of neuroblastoma cells, plus interleukin 2 and a granulocyte–macrophage colony-stimulating factor. Using 13-*cis* retinoic acid improves the outcome further. The additional therapy was found to improve 2-year event-free survival by 20% and overall survival by 11%.

But more and more treatments have not translated to greater survival benefits. According to Maris, "[survival] rates for the high-risk group have only modestly improved despite dramatic escalations in the intensity of the therapy."

Overall 5-year survival rates for neuroblastoma patients have increased from 52% in 1975–1977 to 75% in 1999–2005, but most of that improvement occurred at the lower end of the risk scale. "Over the last 10–15 years, we have been reducing therapy for that group," said Cohn. "Their improved outcome is largely due to the fact that they used to suffer from the toxicity of the more intensive therapy." A study by Cohn published in 2010 in the *New England Journal of Medicine* showed that 3-year survival was 98% among intermediate-risk children with less therapy.

Zage put it another way: "Over the past 20 years, there haven't been a lot of new drugs approved for treatment of pediatric cancer in general." So improvement in survival, says Zage, is primarily due to better combinations of current drugs, an improved understanding of the side effects of current drugs to anticipate and prevent complications, and a better classification of tumors to identify which patients need more or less aggressive therapy.

"We're pretty good at identifying which patients have high-risk neuroblastoma, but we treat all these children the same," said Zage. "Clearly, there are children in this group who do well and survive and are cured, and there are children whose tumors relapse or that don't respond to therapy at all. We don't have a good way of identifying those different forms of neuroblastoma at the outset."

So today's treatment challenge is to identify which high-risk children will respond to the intense therapy and which will not, as well as to find new therapies that will work for the nonresponders.

Treatment Options

Zage's main research interest is to identify new treatments for neuroblastoma in the laboratory. He reported some promising preclinical findings with the drug vandetinib, a tyrosine kinase inhibitor that affects multiple targets. "Instead of hitting one target, most tyrosine kinase inhibitors hit multiple targets and are more nonspecific than we thought," said Zage. "This [finding] may prove to be beneficial for treating cancer, since tyrosine kinases generate multiple signals that drive the growth and spread of cancer cells." The hope is that the right combination of kinase inhibitors will be more effective than inhibiting any one pathway.


Susan L. Cohn, M.D.

Two other classes of kinase inhibitors are already in phase II clinical trials. An ALK inhibitor, known as PF-02341066, targets anaplastic lymphoma kinase proteins that are overexpressed in hereditary neuroblastomas as well as in 5%–15% of sporadic neuroblastoma cases. MLN8237, an inhibitor of aurora kinase A and an important regulator of a cell cycle checkpoint, is being tested in children whose neuroblastomas have recurred or that do not respond to standard therapies.

Several trials are focused on improving therapies that have already proven effective. Investigators are looking to see whether replacing 13-*cis* retinoic acid with fenretinide, another retinoid, is more effective, or whether attaching interleukin 2 to a GD2 monoclonal antibody, rather than administering it separately, improves survival. Other antibodies

against neuroblastoma are being used to deliver radiation directly to the tumors. Researchers are also experimenting with a synthetic norepinephrine-like molecule, MIBG, which neuroblastoma cells take up, thereby increasing the levels of toxic radiation delivered to tumors.

Another strategy is to enlist the immune system to target the tumors. Researchers have engineered several oncolytic viruses—such as Newcastle Disease virus, vaccinia virus, and herpes simplex virus—to selectively destroy tumor cells. Other researchers are hoping to activate the immune system by administering a vaccine consisting of neuroblastoma cell lines engineered to secrete cytokines. Other efforts focus on investigating the effectiveness of inhibitors to certain molecules involved in carcinogenesis, such as proteases, histone deacetylase, and angiogenesis factors.

The Promise of Genetics

Many scientists look to genetics to find less toxic and more targeted future therapies. Already, microarray technology for RNA and DNA analysis of tumors has revealed certain patterns that can predict outcomes.

Maris said that genetics will probably allow researchers to discover most of the critical mutations that cause neuroblastoma or influence its natural history. "This will allow us to identify the key molecular targets for rational drug development. Then, with our rich history of international collaborations, we will test these new approaches in carefully controlled clinical trials. In the end, we should have more precise and effective agents."

The multidrug transporter genes, ABCCs, may prove to be important predictors of outcome and targets for drug development, as reported in a study by Michelle Haber of the Children's Cancer Institute in Randwick, Australia, in this issue of the Journal.

Meanwhile, pediatric oncologists now have more than 100 clinical trials for treating their patients. "It's almost an overabundance of options, and it makes choosing the best trials for individual patients very challenging," said Zage. "But having too many options is always better than too few."

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