Updates in the Management of Neuroblastoma
Presented by Rochelle Bagatell, MD

ABSTRACT

Treatment of children with neuroblastoma depends on accurate assessment of the risk of relapse. Factors used in risk stratification for patients with neuroblastoma include disease stage, MYCN amplification status, age, tumor histology, presence or absence of segmental chromosome aberrations, and tumor cell ploidy. The goal of treatment for patients with low-risk neuroblastoma is cure with minimal toxicity. However, for those with high-risk neuroblastoma, the treatment approach involves multiple therapeutic modalities, including multi-agent chemotherapy at conventional doses, surgery, high-dose chemotherapy with autologous stem cell rescue, external-beam radiotherapy, a differentiating agent, and immunotherapy. Multidisciplinary collaboration is essential for optimal care.

“Neuroblastoma is clinically and biologically a very heterogeneous disease, so it is important to think about risk classification when approaching a newly diagnosed child with neuroblastoma,” commented Rochelle Bagatell, MD, Solid Tumor Section Chief, Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, and Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania, at the NCCN 2024 Annual Conference. Dr. Bagatell is also Chair of the NCCN Guidelines Panel for Neuroblastoma. The prognosis for patients with very low-risk disease is excellent with limited therapy or even observation alone in specific subsets, although outcomes remain poor for many patients with more aggressive disease.

Risk Classification

“When we approach risk classification for a patient, we think first about the INRG [International Neuroblastoma Risk Group] stage,” Dr. Bagatell stated. For patients with localized disease, stage (L1 vs L2) is determined based on the presence or absence of image-defined risk factors. For patients with metastatic disease, stage (M or MS) is determined based on patient age and the pattern of metastatic disease.

For patients with stage L1, L2, or MS neuroblastoma, the first branch point of the risk classification algorithm focuses on MYCN status (amplified or nonamplified). Patients with stage L2 or MS disease whose tumors are found to be MYCN-amplified are classified as having high-risk disease. However, she noted, things become “a bit more complicated” for some other children. For example, for patients with stage L2 (localized with image-defined risk factors) disease whose tumors are not MYCN-amplified,
the cohort of infants who can be safely observed? Can we decrease exposure to chemotherapy and/or decrease surgical morbidity in those who are likely to do well? Are there groups of patients currently treated as high-risk who should be considered non–high-risk?

**High-Risk Neuroblastoma**

**Initial Therapy: Induction and Consolidation**

For patients with high-risk neuroblastoma, “therapy is maximally intensive and involves multiple modalities,” said Dr. Bagatell. “Patient outcomes have improved throughout the decades.” In the 1990s, the survival rate at 5 years was approximately 25%, while the survival rate now is just above 50%.4 However, Dr. Bagatell admitted, “That is not really where we want to be.”

The current approach to treating children with high-risk neuroblastoma follows the conceptual outline shown in Figure 1. Initial treatment includes induction chemotherapy and surgery. Operations performed to remove the primary tumor can be challenging, and a best safe resection approach is recommended. Fortunately, she noted, a large number of patients (~80%) do respond to induction chemotherapy and surgery; however, outcomes are worse for those who do not achieve at least a partial response at the end of induction.5

Patients with a good response to induction proceed to consolidation, which consists of high-dose chemotherapy and stem cell rescue followed by radiotherapy. The medical literature includes several randomized studies that support incorporation of high-dose chemotherapy with autologous stem cell transplantation (ASCT), she said.6–8 The long-term morbidity associated with tandem transplants is a major concern, however. Because the studies showing a benefit with ASCT were conducted at a different time and in a different therapeutic context from where we are now, Dr. Bagatell raised the question as to whether ASCT is still needed in this patient population.

In light of the short, intermediate, and long-term ASCT-related adverse events experienced by children treated for high-risk neuroblastoma, Dr. Bagatell questioned, “Would other strategies be preferred at the current time? Has the addition of immunotherapy to the regimen for patients with high-risk neuroblastoma obviated the need for high-dose chemotherapy with stem cell rescue? Biomarkers to guide treatment selection would be very helpful, and many colleagues in the field are working on this.”

Neuroblastoma is a radiation-sensitive disease, so radiotherapy has a key role in neuroblastoma treatment. Although it is administered at lower doses than are commonly used for other tumors in children, such as sarcoma, questions remain as to the extent of radiation required and the optimal radiation modality to be used. “We have learned from experience that radiotherapy to the primary tumor bed is very important,” according to Dr. Bagatell. “In North America, standard care also includes external-beam radiotherapy to sites of persistent metastatic disease detected at the end of induction therapy, while in much of Europe only the primary tumor is radiated.” More remains to be learned about the risks and benefits of metastatic site radiation.

**Immunotherapy and Targeted Agents for High-Risk Disease**

**Anti-GD2 Antibody Therapy**

“In post-consolidation therapy, the addition of immunotherapy directed at the disialoganglioside GD2 on the surface of neuroblastoma cells has really been a game-changer,” Dr. Bagatell said. “It is a very effective way to harness the body’s own immune system to treat neuroblastoma.” Based on studies performed around the world, anti-GD2–based therapy has become part of the standard regimen for high-risk disease. Current practice in North America is to administer granulocyte macrophage colony-stimulating factor (GM-CSF) in combination with dinutuximab—an anti-GD2 monoclonal antibody—rather than alternating with GM-CSF and interleukin-2, stated Dr. Bagatell. “Patients, families, and providers certainly appreciate this change, because the patients are much less sick and have a lot less capillary leak syndrome and hypoxia. Generally, this therapy is now much better tolerated than it was in the original clinical trial,” she noted.

The use of anti-GD2 therapy has been studied in combination with other agents. For example, in the

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**Figure 1.** High-risk therapy: standard paradigm.
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COG trial ANBL1221 for patients with relapsed/refractory neuroblastoma,9 patients received irinotecan and temozolomide as a backbone and also received targeted agents (either temsirolimus or dinutuximab + GM-CSF). “To our surprise, patients given the irinotecan, temozolomide, and dinutuximab combination had a response rate that exceeded 40%,” Dr. Bagatell reported.

Anti-GD2 antibody therapy is also being investigated in induction therapy. “If it works well in post-consolidation and in the relapsed/refractory setting, why not bring it up-front and try to improve outcomes?” she asked. Outcomes from small studies have been promising, Dr. Bagatell noted, and the addition of dinutuximab to induction chemotherapy is currently being studied in a multicenter COG study, ANBL2131 (ClinicalTrials.gov identifier: NCT06172296). A trial that is currently in the planning stages will next address whether immunotherapy combined with low-dose chemotherapy can be used instead of high-dose chemotherapy with stem cell rescue during consolidation. In the current NCCN Guidelines, high-dose chemotherapy with stem cell rescue remains the standard of care, but the results of a randomized trial to address this issue will be important.

Targeted Therapies

Another question posed by Dr. Bagatell was whether targeted agents might improve outcomes in combination with standard therapy for patients with high-risk disease. According to a recent study by Goldsmith et al,10 the second-generation ALK inhibitor lorlatinib (alone and in combination with chemotherapy) seemed to be active in patients with relapsed/refractory ALK-driven high-risk neuroblastoma, particularly in older patients. COG ANBL1531 is currently evaluating the role of lorlatinib administered in addition to standard multi-modality therapy in newly diagnosed high-risk patients (ClinicalTrials.gov identifier: NCT03126916). The use of the targeted radiopharmaceutical 131I-MIBG (meta-iodobenzylguanidine) is also being evaluated in the same trial. Studies have demonstrated response rates with 131I-MIBG of >30% in the relapsed/refractory setting.11,12 According to Dr. Bagatell, this radio-pharmaceutical allows for targeted systemic radiotherapy because it is taken up by specific transporters on neuroblastoma cells but does not enter normal cells as readily. “Basically, it is like liquid radiation reaching all sites of neuroblastoma involvement in the body,” she explained.

Difluoromethylornithine

Difluoromethylornithine (DFMO), an ornithine decarboxylase inhibitor, received FDA approval in December 2023 to reduce the risk of relapse in adults and children with high-risk neuroblastoma who have shown at least a partial response to prior multiagent therapy including anti-GD2 immunotherapy. Based on recently published analyses using data from patients treated on a single-arm phase II trial compared with data from patients treated on another trial (COG ANBL0032),13 the risk of relapse was reduced in patients who received DFMO for 2 years of continuation therapy after completion of immunotherapy. According to the NCCN Guidelines for Neuroblastoma, clinicians should discuss DFMO as a treatment option with patients and families.

Disclosures: Dr. Bagatell has disclosed no relevant financial relationships.

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References