Neuroblastoma is a pediatric malignant tumor of the postganglionic sympathetic nervous system that usually develops in the adrenal gland or in nonadrenal abdominal or thoracic sites.[1] It is the most common malignancy in infants and the most common extracranial solid tumor of childhood, with approximately 650 cases diagnosed annually in the United States.[2] The dramatic age-related survival differences among neuroblastoma patients with a similar tumor stage emphasize the heterogeneity of neuroblastoma pathobiology. Early research efforts to understand the pathobiology of neuroblastoma[3-5] and the significant progress made in neuroblastoma molecular biology[6] have informed the clinical treatment of neuroblastoma.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community. It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).* We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study. This month’s installment of Clinical Trials Referral Resource is devoted to clinical trials in neuroblastoma. For patient entry information, see the individual trials.

The adoption of the International Neuroblastoma Staging System (INSS) and International Neuroblastoma Response Criteria (INRC) for the diagnosis, staging, and response to treatment[7] of neuroblastoma has facilitated the incorporation of tumor biological characteristics (favorable and unfavorable) into the development of low-, intermediate-, and high-risk treatment stratification for neuroblastoma clinical trials designed by the Children’s Oncology Group (COG). Newly diagnosed patients are stratified by age (less than or greater than 365 days old) and the tumor’s INSS stage, but tumor tissue analysis is central to determining a patient’s treatment risk stratification (see Table 1). Tumor histology is evaluated using the Shimada histologic classification of favorable or unfavorable biology[8]; molecular biological characteristics of N-myc amplification and DNA ploidy are established prior to treatment selection.
Low-Risk Neuroblastoma

Children with localized neuroblastoma and a favorable tumor biology can usually be cured with surgery alone; chemotherapy and radiotherapy are employed only for progressive or recurrent disease, or for patients diagnosed with spinal cord compression.[9] Although stage 2 patients with incomplete tumor excision or positive ipsilateral lymph nodes have a higher likelihood of local recurrence, the majority of these patients can be salvaged with repeat surgery alone, with an ultimate survival rate of 98%.[9]

In the current Pediatric Oncology Group (POG) legacy study, P9641, for low-risk neuroblastoma, all stage 1 and select stage 2 patients undergo surgery(s) to remove as much of the primary tumor and involved lymph nodes as can be safely resected. Patients whose disease has been greater than 50% resected are systematically observed. If less than 50% of the tumor has been resected or the residual tumor threatens vital organs, then four cycles of outpatient chemotherapy including carboplatin (Paraplatin), etoposide, cyclophosphamide (Cytoxan, Neosar), and doxorubicin are given. Regression of residual disease, without the use of chemotherapy, is expected to occur in the majority of patients whose tumors are incompletely resected at diagnosis.[10] If progressive or recurrent disease is observed in any patient, reoperation is attempted. If low-risk disease is again completely resected, the patient is systematically observed; otherwise, four courses of chemotherapy are administered.

Intermediate-Risk Neuroblastoma

Children with advanced regional neuroblastoma represent a biologically heterogeneous group of patients. Clinical trials have shown that stage 3 infants with nonamplified N-myc and older children with nonamplified N-myc and a favorable histopathology treated with low-intensity combination chemotherapy, eventual gross total tumor resection, and/or local radiotherapy[11] can achieve an excellent outcome (4-year event-free survival of 100%). Selected infants with disseminated neuroblastoma (stage 4 with favorable biology)[12] are treated with less intensive adjuvant chemotherapy, while stage 4S patients can be treated with supportive care or low-dose cytotoxic therapy if symptomatic[13,14] and have an excellent outcome.

For infants and children with intermediate-risk neuroblastoma, COG protocol A3961 recommends surgery to remove as much of the primary tumor and involved lymph nodes as can be safely resected with minimum morbidity. Patients then receive four cycles of chemotherapy, as in P9641 if the tumor is of favorable biology, and eight cycles of chemotherapy if the tumor is of unfavorable biology.

High-Risk Neuroblastoma

A randomized study has demonstrated that high-dose chemotherapy and radiotherapy followed by transplantation of autologous bone marrow is superior to conventional chemotherapy as consolidation therapy in children with high-risk neuroblastoma[15] with a 34% vs 22% 3-year event-free survival, respectively. The addition of 6 months of maintenance therapy using 2-week cycles of the differentation agent 13-cis-retinoic acid (13-cis-RA) was of benefit in both the autologous bone marrow transplant and conventional chemotherapy treatment groups with a 3-year event-free survival of 46% for those receiving 13-cis-RA vs 29% for those assigned no further therapy.

Investigations have been under way to incorporate immunotherapy as treatment of minimal residual disease in children with high-risk neuroblastoma after induction and consolidation therapy. Antibodies targeting the GD2 glycoside, commonly expressed on neuroblastoma cells, can be safely administered to children[16,17] in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), and there is evidence that such treatment can clear residual neuroblastoma from the bone marrow.

Among high-risk patients, the current COG phase III study, A3973, is designed to determine the event-free survival and toxicity of a myeloablative consolidation with infusion of autologous purged peripheral blood stem cells (PBSC) vs unpurged PBSC followed by local radiotherapy. A dose-intensive induction therapy using six cycles of cyclophosphamide, doxorubicin, and vincristine alternating with cisplatin (Platinol) and etoposide is being utilized. After completion of CEM chemotherapy (high-dose carboplatin, etoposide, and melphalan [Alkeran]) and stem cell transplant, A3973 patients will be offered enrollment in ANBL0032. The ANBL0032 maintenance therapy study will evaluate whether 13-cis-RA with the addition of five courses of the anti-GD2 monoclonal
antibody Ch14.18 plus GM-CSF/interleukin-2 treatment improves event-free and overall survival as compared to 13-cis-RA alone. Patients in A3971 who refuse or are unable to receive myeloablative therapy will receive maintenance therapy with topotecan (Hycamtin) and cyclophosphamide. Additionally, a limited-institution COG pilot study, ANBL00P1, for high-risk patients is under way to assess the feasibility of tandem high-dose chemotherapy with autologous stem cell rescue as a means of increasing dose-intensive therapy.[18] After completion of induction chemotherapy and collection of peripheral blood stem cells with CD34+ selection, patients will proceed to tandem high-dose intensification using thiopeta (Thioplex) and cyclophosphamide as the first conditioning regimen, and CEM as the second conditioning regimen. Appropriate local radiation therapy will follow completion of the tandem transplants.

Observation for Perinatally Diagnosed Neuroblastoma

The now common use of prenatal ultrasound has led to an increase in the annual incidence of neuroblastoma, mostly adrenal primaries, among infants, from 53.7 million to 73.4 million for 1976-1984 and 1986-1994, respectively.[2] Typically, the infants identified perinatally present with low-stage neuroblastoma that has favorable histopathologic and biological markers.[19] The majority of neuroblastomas identified in infants by screening (97%) have favorable histology tumors, and these tumors are often (76%) stage 1, 2, or 4S, with excellent clinical outcome (survival rate of 98%).[20] It is believed that due to the unique biology of infant neuroblastoma, many of the tumors identified by screening would never have been identified clinically, although the frequency and timing of natural tumor regression is unknown.

While surgical resection has been the usual approach for masses identified either by incidental ultrasound or organized screening, neuroblastoma in infants can regress spontaneously without intervention.[21] Surgical series of infants diagnosed prenatally with suprarenal masses suggest that observation of the mass in anticipation of tumor regression may be an appropriate strategy[22]; however, there are multiple cases in the literature of early-identified neuroblastomas that were aggressive and ultimately fatal.[9,23,24]

A COG pilot study, ANBL00P2, is now under way to determine whether nonoperative management with close biochemical and sonographic observation will result in acceptable outcomes for patients with adrenal masses discovered on prenatal and/or perinatal ultrasound examinations. In this study, surgical resection is reserved for those with evidence of continued growth. The study will use a prospective, single-arm design. Any increase in tumor volume or catecholamine secretion above a threshold level will trigger more frequent surveillance, followed by surgical resection if growth continues.

Relapsed/Recurrent Neuroblastoma

Children with high-risk neuroblastoma usually respond initially to multimodality therapy, but many ultimately develop recurrent tumor that is refractory to further treatment. The New Approaches to Neuroblastoma Therapy (NANT) Consortium has two active experimental studies for children with progressive or relapsed neuroblastoma. NANT 99-01 is a dose escalation study of 131I-metaiodobenzylguanidine (MIBG), a norepinephrine analog that concentrates in adrenergic tissues and neuroblastoma cells.[25] This radioactive treatment is followed by the CEM conditioning regimen with autologous stem cell rescue and subsequent local radiotherapy administered as needed.

NANT 99-02 is investigating the combination of buthionine sulfoximine (BSO) and melphalan[26] for overcoming alkylator resistance in relapsed neuroblastoma patients. Patients receive a standard dose of BSO and an escalating dose of melphalan followed by autologous stem cell rescue.[27] The goal is to determine the maximum melphalan dose that can be administered in the context of BSO-induced intracellular glutamine depletion and stem cell rescue.

Future Directions

New treatment approaches for neuroblastoma to be piloted as supplements to traditional cytotoxic chemotherapy include immunotherapy with the anti-GD2 interleukin-2 fusion protein[28] and the use of retinoid derivatives such as fenretinide.[29] Clinical markers of tumor response and residual disease, using bone marrow immunocytochemistry or reverse transcriptase-polymerase chain reaction detection of tumor cells in stem cell products, are under investigation in the current COG protocols and may someday influence treatment decisions for individual patients, especially in those with
advanced disease. Molecular studies, facilitated by the companion neuroblastoma biological study, ANBL00B1, will investigate the impact of additional biological factors on clinical outcomes. The potential prognostic significance of TrkA and TrkB neurotrophin receptor expression[30] and the expression of other tyrosine kinase receptors, particularly the EPH family[31] and their ligand ephrins, are under study. Additionally, investigations of chromosome loss, such as 1p, and evidence of genomic instability are to be conducted on collected tumor tissue.[6,32] It is hoped that the continued elucidation of neuroblastoma pathobiology will allow continued refinement of the treatment of neuroblastoma and will direct the best use of future molecularly targeted therapies.

**Phase III**

**Title:** Phase III Study of Combination Chemotherapy in Children With Intermediate-Risk Neuroblastoma  
**Protocol Number:** CCG-A3961  
**Participating Institutions:** Children's Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase III Randomized Study of Purged Versus Unpurged Peripheral Blood Stem Cell Transplantation Following Dose Intensive Induction Chemotherapy in Patients With Newly Diagnosed High Risk Neuroblastoma  
**Protocol Number:** CCG-A3973, CCG-39703  
**Participating Institutions:** Children's Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase III Randomized Adjuvant Study of Isotretinoin With or Without Monoclonal Antibody Ch14.18, Interleukin-2, and Sargramostim (GM-CSF) in Patients With High-Risk Neuroblastoma Who Have Completed Myeloablative Therapy and Autologous Stem Cell Transplantation  
**Protocol Number:** COG-ANBL0032, COG-P9842  
**Participating Institutions:** Children's Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase III Study of Primary Surgical Therapy in Children With Low-Risk Neuroblastoma  
**Protocol Number:** POG-P9641  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)  

**Phase I**

**Title:** Phase I Study of hu14.18-Interleukin-2 Fusion Protein in Children With Refractory or Recurrent Neuroblastoma or Other GD2-Positive Tumors  
**Protocol Number:** COG-ADV0018, CCG-ADV0018, POG-ADV0018  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of Iodine I 131 Metaiodobenzylguanidine Plus Intensive Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation in Patients With Refractory or Residual High-Risk Neuroblastoma  
**Protocol Number:** CHLA-LA-NANT-99-01, NCI-V00-1592  
**Participating Institutions:** New Approaches to Neuroblastoma Therapy (NANT)  
**Contact:** Beth Hasenauer, RN, MS, (323) 669-5687; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)  
**Latest Information:** [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of Melphalan and Buthionine Sulfoximine in Children With Recurrent or Refractory High-Risk Neuroblastoma  
**Protocol Number:** CHLA-LA-NANT-99-02, NCI-68  
**Participating Institutions:** New Approaches to Neuroblastoma Therapy (NANT)  
**Contact:** Beth Hasenauer, RN, MS, (323) 669-5687; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)
Current Clinical Trials in Neuroblastoma

Published on Physicians Practice (http://www.physicianspractice.com)

Latest Information: http://www.cancer.gov/clinical_trials/

Pilot Studies

Title: A Pilot Study of Tandem High-Dose Chemotherapy with Stem Cell Rescue Following Induction Therapy in Children with High-Risk Neuroblastoma

Protocol Number: ANBL00P1

Participating Institutions: Children’s Oncology Group

Contact: Judith Everett, (626) 447-0064, ext 116

Title: Perinatal Neuroblastoma: Expectant Observation: A Children’s Oncology Group Pilot Study

Protocol Number: ANBL00P2

Participating Institutions: Children’s Oncology Group

Contact: Judith Everett, (626) 447-0064, ext 116

Other Studies

Title: Neuroblastoma Biology Studies

Protocol Number: ANBL00B1

Participating Institutions: Children’s Oncology Group

Contact: Judith Everett, (626) 447-0064, ext 116

References:


Source URL: http://www.physicianspractice.com/review-article/current-clinical-trials-neuroblastoma

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