Can you provide some background on neuroblastoma?

SM Neuroblastoma, a tumor of sympathetic nervous tissue, is a rare childhood disease. There are about 700 new cases diagnosed per year in the United States, which is equivalent to about 10 per 1 million children per year. Neuroblastoma is the most common extracranial solid tumor in infants, but it is still a relatively rare disease. Survival depends on stage of disease at diagnosis. Locoregional neuroblastoma that is non–stage IV generally has a very good outcome, with a cure rate of approximately 90%, unless there is amplification of the MYCN oncogene. Most patients who present with stage 4 disease—about half of the patients at diagnosis are stage 4—below the age of 18 months do very well with relatively modest chemotherapy. These patients have survival rates in excess of 90%. However, children over 18 months of age with stage 4 disease have a much poorer outcome. Published studies have demonstrated a cure rate for these patients of approximately 30–35%. Five-year overall survival is much higher, with a rate of approximately 50%. Over the last 10 years there have been significant advances in treatment for neuroblastoma. At our center, we now expect half of the patients with stage 4 disease who are older than 18 months at diagnosis to survive.

How is neuroblastoma diagnosed? What are the common signs and symptoms?

SM In stage 4 disease, the most common presentation is nonspecific symptoms including irritability, limp, fevers, and bone pain. In locoregional neuroblastoma, diagnosis is often made accidentally when patients are seen for other reasons by a pediatrician and an abdominal mass is palpated. Sometimes a chest X-ray is done and a thoracic mass is accidentally observed. Rare presentations include paraplegia in patients who have para spinal neuroblastoma. Patients can also present with a rare syndrome called opsoclonus myoclonus syndrome, in which they experience ataxia, myoclonic jerks, and nystagmus. Another uncommon presentation is severe profuse diarrhea, which is associated with secretion of vasoactive intestinal peptide. Finally, children can present with hypertension due to the presence of elevated urinary catecholamines.

There is a rare, spontaneously resolving entity called stage 4-S neuroblastoma; patients may present with stage 4-S disease in the newborn period or in early infancy with significant hepatic enlargement, and may even develop respiratory distress due to the hepatic enlargement. This is sometimes associated with skin nodules, called the blueberry muffin rash.

The diagnosis of neuroblastoma is confirmed either by biopsy of the primary tumor—which is usually adrenal or abdominal, but may also be thoracic, pelvic, or cervical—or by demonstration of an elevated urinary catecholamine level in addition to the presence of bone marrow metastasis. Besides tests for anatomical definition such as computed tomography or magnetic resonance imaging, the metaiodobenzylguanidine (MIBG) scan, which is currently the gold standard diagnostic test, is also performed. The MIBG scan is a nuclear medicine scan, which can detect primary and metastatic disease in more than 90% of patients. Finally, bone marrow testing at multiple sites may also be performed to establish diagnosis and staging. Biopsy and aspiration are the 2 ways of sampling bone marrow.
**H&O** How are predictive and prognostic markers involved in diagnosis and treatment?

**SM** The most important prognostic markers are age and stage. Stage 4 neuroblastoma in a child older than 18 months is associated with a much poorer prognosis than in a patient younger than 18 months. Non–stage 4 patients, regardless of age, have a much better prognosis. Stage 4-S neuroblastoma has a good prognosis because it is a type of disease that spontaneously resolves without any treatment.

Other prognostic markers include the MYCN oncogene. Amplification of this oncogene was an independent poor prognostic marker in the days before high-dose induction chemotherapy but not since the advent of such chemotherapy. For locoregional neuroblastoma, besides MYCN gene amplification, prognostic markers include DNA index, with diploid tumors having the worst prognosis. Histology is another marker; the definition of unfavorable histology can be made by microscopic examination, and is associated with worse prognosis. Some other prognostic markers that are being prospectively studied are 11q deletions and 17q gain in locoregional disease. Also, serum lactate dehydrogenase and serum ferritin levels and the ratio of urine vanillyl mandelic acid to homovanillic acid are also considered to be part of the prognostic workup.

**H&O** What are the current treatment approaches in neuroblastoma?

**SM** The components of treatment include induction chemotherapy, surgery, radiation therapy, and anti-GD2 therapy. The treatment for locoregional neuroblastoma is resection of the tumor. There are several treatment approaches currently being studied. At Memorial Sloan-Kettering Cancer Center (MSKCC), patients with locoregional disease for tumors that are not MYCN amplified are treated with surgery alone. Another approach, which is being studied by the Children's Oncology Group (COG), involves the administration of low doses of chemotherapy prior to surgery for non-MYCN amplified tumors. Radiation is not required for these patients. For locoregional disease that is associated with an MYCN amplification and for stage 4 disease at age greater than 18 months, regardless of MYCN amplification, the treatment is very high doses of chemotherapy for induction followed by surgical resection and then radiation to prevent local recurrence. To prevent systemic recurrence, autologous transplant either preceded by myeloablative chemotherapy or followed by antibody therapy targeted to the GD2 antigen is administered. At MSKCC, patients who achieve remission after induction chemotherapy and surgery are given immunotherapy without going through myeloablative chemotherapy.

In addition to myeloablative chemotherapy, immunotherapy with 2 anti-GD2 antibodies can be used to prevent systemic recurrence. Chimeric antibody 14.18 (ch 14.18) has recently been studied in a phase III trial, which was terminated prior to completion because the randomized arm receiving ch14.18 had significantly improved progression-free survival at 2 years. Ch14.18 is now considered the standard of care after transplant. Ch14.18 has also been administered along with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 2 (IL2). Preliminary data on this combination have been reported in the *New England Journal of Medicine*. The findings showed that the combination of ch14.18, GM-CSF, IL2, and cis-retinoic acid was associated with better outcome in progression-free survival and overall survival when compared to patients who did not receive ch14.18 in combination with the cytokines.

The other anti-GD2 antibody that has been extensively used is 3F8. It has been utilized primarily at MSKCC in conjunction with GM-CSF. Antibody 3F8 plus GM-CSF has been investigated in a phase II study at our institution; the findings showed a long-term event-free survival of 50–55% in patients who received 3F8 in first remission, thus the follow-up is longer in patients who have received 3F8.

**H&O** Can you discuss some chemotherapy regimens used for neuroblastoma treatment?

**SM** Induction chemotherapy consists of very high doses of multiagent regimens. Alkylating agents like cyclophosphamide are the mainstay of treatment. Other agents include doxorubicin, anthracyclines, vincristine, cisplatin, and etoposide. The COG has piloted a recent study in which cyclophosphamide and topotecan in intermediate doses are given as upfront treatment. For myeloablative chemotherapy, regimens have included total body radiation, melphalan, carboplatin, busulfan, and etoposide. There does not appear to be a role for maintenance chemotherapy in preventing relapse. However, local radiation therapy is required for prevention of local recurrence; it is typically administered at a dose of 2100 Gy for patients who do not have any visible residual disease.

**H&O** What data do we have in patients with recurrent disease?

**SM** At least half of neuroblastoma patients will recur despite being in remission and having regular scans that show no evidence of disease. There are several therapeutic options available for patients who relapse or...
who do not achieve remission; these treatments include second-line chemotherapy with agents such as topotecan, irinotecan, temozolomide, or ifosfamide, and carboplatin and high-dose cyclophosphamide plus irinotecan or topotecan. Non-chemotherapeutic options for resistant disease include MIBG therapy. The combination of 3F8 and GM-CSF is associated with encouraging results in patients who have achieved a second remission with chemotherapy.

There are several agents being tested in phase I and II studies. An ALK inhibitor targeting the ALK gene, which is mutated in a very small group of neuroblastoma patients, is currently in early studies. MIBG therapy in conjunction with radiation sensitizers such as arsenic, irinotecan, and vorinostat is also being tested. Researchers are evaluating cell therapies targeting T cells and NK cells in neuroblastoma. Anti-GD2 vaccine approaches as well as autologous vaccines directed against neuroblastoma, often using T cells that have been transfected with chimeric antigen receptors, are being tested.

H&O What are the challenges that pediatric oncologists face in treating neuroblastoma?

SM In the past, the challenge was curing patients; curing stage 4 patients was considered extremely difficult, if not nearly impossible. Now, with the advent of higher dose induction chemotherapy and strategies to prevent recurrence, the majority of patients with stage 4 neuroblastoma are surviving. Oncologists now face different challenges than they did in the past, mainly concerning secondary effects of chemotherapy, such as growth delays, cardiotoxicity from the use of anthracyclines, hearing loss, secondary malignancies to the chemotherapy, and learning disabilities. We are also seeing a new syndrome of isolated central nervous system recurrence—recurrence in the brain without recurrence elsewhere. In the past, these recurrences were lethal, but now, with a new strategy that has been pioneered at MSKCC, at least half of the patients who recur with central nervous system disease can be salvaged. This strategy involves the use of radioimmunotherapy that is targeted to the central nervous system via intrathecal injections. In a disease that used to be fatal in 100% of patients, with a median survival of 7–8 months, the natural history has now been changed so that most patients can actually be cured, or at least achieve long-term remissions.

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