Neuroblastoma and brain tumors in childhood

Joann L. Ater, MD

The treatment of childhood cancer requires a multidisciplinary approach to provide the best quality of life and chance of survival. This is most apparent in children with central and peripheral nervous system tumors where tumor and therapy can result in significant morbidity even for those who survive. Table 1 shows the extensive list of health care professionals required to treat most children with brain tumors, and to some degree for children with other solid tumors such as neuroblastoma. This paper will focus on the incidence, diagnosis, prognosis, and treatment of children with central nervous system (CNS) tumors and neuroblastoma. Rather than focusing upon the specific chemotherapy protocols, this discussion will emphasize information essential for members of the multidisciplinary team whose primary field is other than pediatric oncology or neuro-oncology and emphasize supportive care. More in-depth discussions of current chemotherapy are available in several recent reviews.[1,2]

TABLE 1. PEDIATRIC ONCOLOGY MULTIDISCIPLINARY CARE TEAM

Pediatric oncologist	Pediatric dentist
Pediatric neurologist	Endocrinologist
Radiotherapist	Ophthalmologist
Neurosurgeon	Rehabilitation specialist
Pediatric surgeon	Audiologist
Pediatric neuropsychologist	Pathologist
Child psychiatrist	Neuroradiologist
Pediatric nurse	Pediatric anesthesiologist

Incidence and prognosis

Brain tumors are the second most common childhood cancer comprising 25% of neoplasms diagnosed in children younger than 16 years old. Each year in the United States, more than 2,000 children younger than 19 years old are diagnosed with brain tumors. Neuroblastoma, an embryonal tumor of the sympathetic nervous system, is the third most common solid tumor, comprising 8% of neoplasms. Neuroblastoma can arise anywhere along the paraspinal sympathetic chain from the pelvis to neck or within the adrenal gland. Metastasis at diagnosis is common, usually to liver, bone, bone marrow, and orbits. Both neuroblastoma and brain tumors have peak incidence in early childhood (2 to 4 years of age). Also, both neuroblastoma and brain tumors share the dubious distinction of having the lowest overall 5-year survival rates (50–60%) of all the solid tumors. In addition progress in improving survival has lagged behind that achieved in other types of childhood cancer over the last two decades.[3]

Progress in treating brain tumors has lagged behind partly because in children there are many difficult histologic types of brain tumors, which vary widely in tumor biology, aggressiveness, and response to therapy. In addition, even within a single histologic diagnosis, such as astrocytoma, the prognosis can vary dramatically depending upon the site of origin in the brain and tumor grade (Table 2). For example, low-grade astrocytoma in the cerebellum carries a 95% survival rate,[4] while a low-grade astrocytoma of the hypothalamus carries only a 40–60% survival rate. Because of this wide variation, it has not been possible to develop a

TABLE 2. PROGNOSIS OF CHILDHOOD BRAIN TUMORS

Tumor/Grade	*Site/Grade*	*5-Year Survival*
Low-grade astrocytoma	Cerebellum	95%
	Cerebral hemisphere	70%
	Hypothalamus/midbrain	40–70%
	Brain-stem-dorsally exophytic	90%
Anaplastic astrocytoma	Supratentorial	10–44 %
Glioblastoma multiforme	Resectible	30%
	Unresectible	0%
Medulloblastoma	Average risk	60%
	High risk	40%
Brain-stem glioma	Pontine	10%
Ependymoma	All sites	60%

unified approach to management. For example, Childrens Cancer Group currently has 14 proposed and open therapeutic protocols for treating brain tumors. Because of the small number of children available for each study, it often takes many years to reach statistical significance. In addition, while 95% of children with cancer participate in protocol studies, far fewer children with brain tumors are referred for protocol therapy. However, even with controlled clinical trials, some tumors such as high-grade astrocytomas and brain-stem gliomas remain resistant to most therapeutic modalities and overall cure rates are poor (Table 2).[5]

Neuroblastoma, although a single tumor type, also varies widely in its behavior depending upon the child's age and extent of disease at diagnosis, and presence of N-myc oncogene amplification. Children younger than 1 year old and those with low-stage disease have a greater than 80% survival rate while those with advanced stage metastatic disease (stage IV), have less than 20% chance of survival.

Brain tumors

Diagnosis

The clinical presentation of children with brain tumors depends primarily on the site of tumor in the nervous system. The majority of tumors in children are in the posterior fossa near the fourth ventricle, leading to early obstruction of the cerebral spinal fluid pathway and hydrocephalus. The symptoms of hydrocephalus are headache, vomiting, somnolence, and diplopia. Its location in the cerebellum also leads to ataxia and imbalance. Tumors in the cerebral hemispheres can be more silent, presenting with hemiparesis, change in school performance, headache, lethargy, or vomiting. In children, tumors of midline structures including hypothalamus, optic chiasm, thalamus, and pineal area have specific ocular and neurobehavioral problems at diagnosis. Tumors of the pineal area present with symptoms of hydrocephalus and specific findings of paralysis of upward gaze and poor convergence. In addition, tumors of midline, which involve the hypothalamus or suprasellar region (germinomas, optic chiasmal astrocytomas, and craniopharyngiomas), frequently present with symptoms of endocrine dysfunction such as diabetes insipidus, precocious puberty, growth deficiency, and eating disorders.[6]

Diagnosis is made by computed tomography (CT) scan or magnetic resonance imaging (MRI). Although dental appliances can cause artifacts in the frontal region of the brain on an MRI scan, it is usually not necessary to remove braces because few childhood tumors are located in this region. Once a tumor is identified using imaging, surgical resection usually is performed to provide histologic diagnosis and therapy. Where significant resection is not feasible because of location, (e.g., thalamic gliomas), stereotactic or open biopsies can provide diagnostic tissue to guide therapy and predict prognosis. For brain-stem gliomas intrinsic to the pons, the MRI is diagnostic and biopsy is not recommended.

Therapy

In treating children with brain tumors, the primary goal is to achieve cure with minimal morbidity. For young children, because of their immature, developing nervous systems, the risk of morbidity of therapy is high. In addition, the overall prognosis in children younger than 4 years old with malignant brain tumors is worse than for older children.[7] Therefore, beginning in 1976, van Eys at the University of Texas M.D. Anderson Cancer Center began treating young children with brain tumors with a multidisciplinary approach designed to control the tumor and delay or avoid radiotherapy. This approach consists of: 1) as aggressive a surgical resection as possible without increasing neurological impairment; 2) delaying radiotherapy in children younger than 4 years old until tumor progression subsequent to an alternative treatment. For low-grade tumors children receive surgical resection alone or chemotherapy for progressive or incompletely resected tumors. For high-grade tumors, chemotherapy is given within 1 month after initial surgery. In van Eys' initial program, MOPP chemotherapy was utilized.[8] More recently, other groups such as the Pediatric Oncology Group (POG) have utilized other chemotherapy.[9] With chemotherapy in young children with medulloblastoma the 5-year survival rate in the MOPP treated group was 67%. In addition, children who had surgical management with or without chemotherapy had significantly higher IQ levels and fewer growth deficiencies than age-matched children treated with radiation therapy.[10]

Some older children still receive either surgery alone or surgery and radiation. However, several randomized trials comparing radiation to chemotherapy have

TABLE 3. RANDOMIZED TRIALS OF ADJUVANT CHEMOTHERAPY (LOMUSTINE, VINCRISTINE ± PREDNISONE) IN CHILDREN WITH BRAIN TUMORS*

Tumor Type	*Year Reported*	*Study Group*	*Benefit from Chemotherapy*
Medulloblastoma	1990[11]	Childrens Cancer Study Group	Yes
Medullobastoma	1990[12]	International Society of Pediatric Oncology	Yes
High-grade glioma	1990[13]	Childrens Cancer Study Group	Yes
Brain-stem glioma	1989	Childrens Cancer Study Group	No
Malignant ependymoma	1989	Childrens Cancer Study Group	No

* In poor-prognosis types.

found improved survival with chemotherapy (Table 3).[11–13] Many studies currently are underway evaluating different chemotherapy regimens for malignant brain tumors and unresectable low-grade tumors. Therefore, children with brain tumors are at risk for oral pathology related to both radiation therapy and chemotherapy with immunosuppression and neutropenia. Finally, a number of clinical trials have begun utilizing high-dose chemotherapy with autologous bone marrow rescue to treat malignant brain tumors. As for any bone marrow transplantation, dental evaluation prior to the transplant is an essential part of therapy because of the extremely high risk of infection during the prolonged period of immunosuppression following transplant.

In addition, children with brain tumors may have other special needs and problems of which the dentist should be aware. Many will receive phenytoin postoperatively to prevent seizures and steroids for increased intracranial pressure. Phenytoin may lead to gingival hypertrophy, and steroids for tumor in the hypothalamic region may lead to functional adrenal insufficiency. For surgical or dental procedures, supplemental steroids may be necessary. About one-third of the children will have a ventriculoperitoneal shunt or central venous catheter, which require antibiotic prophylaxis for dental procedures. Some neurologic dysfunction related to the tumor, such as cranial nerve deficits and poor gag reflex, may make the risk for anesthesia for the procedures a higher risk. Finally, decreased attention span, hyperactivity, and intellectual deficit manifested by some children with brain tumors may make voluntary cooperation for dental work particularly challenging and necessitate anesthesia. Therefore, the pediatric dentist is an essential member of the pediatric neuro-oncology team.

Neuroblastoma

Diagnosis

Neuroblastoma is a tumor of the sympathetic nervous system, and therefore can originate from sympathetic ganglion anywhere along the spine from neck to pelvis and in the adrenal gland. Because of the wide variety of locations, a variety of clinical presentations can occur:

1. A mass in the abdomen, neck, skin or chest
2. Neurologic symptoms due to paraspinal location with cord compression or related to a preneoplastic syndrome seen with neuroblastoma resulting in opsomyoclonus ("dancing eyes") and ataxia
3. Pain related to metastatic disease — unknown fever and weight loss can predominate
4. Some children with metastatic disease to the orbit present with ecchymosis cervical around eyes and at times ptosis.

Diagnosis usually is made by radiographic confirmation of mass and surgical biopsy or resection. In children with metastatic disease and characteristic clinical presentation, the diagnosis previously was made without surgery in children with tumor cells in the bone marrow and elevated urinary catecholamines [homovanillic acid (HVA) and vanylmandelic acid (VMA)] in the urine. Now because of valuable prognostic information obtainable from tissue histology, use of the Shimata classification system,[14] and by obtaining N-myc copy number,[15] children usually have surgical biopsy or resection of their primary tumor. Prognosis is related primarily to age, stage, and Shimata histopathologic classification and N-myc copy number. In addition, children younger than 1 year of age with neuron specific enolase (NSE) elevation have a worse prognosis (Table 3).

Staging

Several systems have been devised for staging children with neuroblastoma. The most commonly used is the Evans system utilized by the Childrens Cancer Group (CCG).[16] In this system, stage I are tumors confined to a single primary tumor mass that is totally resected; stage II is a tumor that cannot be totally resected, but does not cross the midline; stage III is a tumor with residual disease crossing midline structures; and stage IV denotes metastatic disease. A special stage, IVS, is an unusual tumor distribution usually only found in children younger than 1 year of age. These children have a small stage I or II primary, but have widespread soft tissue metastases. Differentiating between stage IV and IVS is essential, since the IVS tumors can spontaneously regress without treatment, and stage IV require aggressive treatment and have poor prognosis. Another staging system utilized by the Pediatric Oncology Group designates stages as A, B, C, D, using slightly different criteria. Because of the difficulty in evaluating clinical studies using different staging systems, a group has been organized to design and test an International Staging System, which would be used worldwide.[17]

Prognosis and therapy

Extensive study of prognostic factors has allowed us to tailor the therapy for low-, average-, and high-risk groups. Table 4 shows the factors that help pediatric oncologists determine prognosis and therapy. Stages I and II, unless N-myc amplification are present, carry an excellent prognosis with a higher than 80% survival rate at 5 years with surgery alone. Even for children with stage II who have a small amount of residual tumor, studies have confirmed that radiotherapy is not necessary.[18] Therefore, for stages I and II treatment is usually surgery alone. For stages III and IV, treatment usually is aggressive chemotherapy. Autologous bone marrow transplantation (ABMT) currently is under investigation and commonly is used for high-risk patients, however, it has not yet been definitively proven in a randomized trial to provide better long-term cure than chemotherapy alone. The problem is that although short-term results in children who initially respond to chemotherapy and then receive transplantation

are encouraging, the long-term survival rate of 10–15% for stage IV may not be improved. Currently, CCG institutions are performing a randomization between transplant and chemotherapy alone for advance stage neuroblastoma.

Radiotherapy is utilized in neuroblastoma primarily for stage III disease (incompletely resected tumor that crosses the midline, without metastatic disease). The five-year survival rate of children with stage III is now 60–70% with aggressive chemotherapy and radiotherapy.[19]

The child with neuroblastoma presents as a challenge to the pediatric dentist because of tumors that can be metastatic or primary to the head and neck region and because of the severely immunosuppressive treatment. The chemotherapy regimens for advance stage neuroblastoma, usually include Adriamycin™ (Adria Laboratories, Columbus, OH), cyclophosphamide, VP-16 (etoposide), and cisplatin, which may result in severe neutropenia and mucositis. Cis-retinoic acid also is included in some neuroblastoma trials as a differentiation agent. This medication frequently leads to dry lips and mouth, which in some patients can produce significant oral discomfort.

TABLE 4. PROGNOSIS AND THERAPY OF NEUROBLASTOMA

Prognosis	*Survival*	*Characteristics*	*Treatment*
Good	96%	Stage I	Surgery
	90%	Stage II (< 10 copies N-myc)	Surgery
	91%	Stage IVS, stable	Observation
		With symptomatic hepatomegaly	XRT, Cytoxan
Intermediate	> 70%	Stage III with favorable histopathology, < 10 copies N-myc	Surgery, chemotherapy
	70%	Stage IV < 1 year with NSE < 100 mg/ml	Surgery, XRT, chemotherapy
Poor	< 30%	Stage II ≥ 10 copies MYC	Surgery, XRT, chemotherapy
	< 20%	Stage III, unfavorable histopathology ≥ 10 copies N-myc	Possible ABMT ± cis-retinoic acid
	< 10%	Stage IV > 1 year	Surgery, chemotherapy, possible ABMT ± cis-retinoic acid

Conclusion

Children with brain tumors and neuroblastoma require multidisciplinary care to improve survival, decrease morbidity and risks of therapy, and provide best quality of survival. The pediatric dentist is an important member of this multidisciplinary team.

Dr. Ater is assistant professor and chief, Pediatric Neural Tumor Section, Department of Pediatrics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

1. Freidman HS, Oakes WJ: New therapeutic options in the management of childhood brain tumors. Oncology 6:27–36.
2. Ater JL: Chemotherapy for pediatric brain tumors. Cancer Bull 45:351–56, 1993.
3. Young JL Jr, Ries LG, Silverberg E, Horn JW, Miller RW: Cancer incidence, survival and mortality for children younger than 15 years. Cancer 58:598–602, 1986. (Suppl 2)
4. Levin VA, Sheline GE, Gutin PH: Neoplasms of the central nervous system. In: Cancer: Principles and Practice of Oncology, DeVita VT Jr, Hellman S, Rosenberg SA, Eds. Philadelphia: JB Lippincott; 1557–1611; 1993.
5. Heideman RL, Packer RJ, Albright LA, et al: Tumors of the central nervous system. In: Principles and Practice of Pediatric Oncology, Pizzo PA and Poplack DG, Eds. Philadelphia: JB Lippincott; 633–81, 1993.
6. Petronio J, Edwards MSB, Prados M, Freyberger S, Rabbitt J, Silver P, Levin VA: Management of chiasmal hypothalamic gliomas of infancy and childhood with chemotherapy. J Neurosurg 74:701–8, 1991.
7. Duffner PK, Cohen ME, Myers MH, Heise HW: Survival of children with brain tumors: SEER program, 1973–1980. Neurology 36:597–601, 1986.
8. van Eys J, Cangir A, Coody D, Smith B: MOPP regimen as primary chemotherapy for brain tumors in infants. J Neuroncol 3:237–43, 1985.
9. Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC, Cohen ME, Sanford RA, Mulhern RK, James HE, Freeman CR: Postoperative chemotherapy and delayed radiation, in children less than 3 years of age with malignant brain tumors. N Engl J Med 328:1725–31, 1780–81, 1993.
10. Moore BD 3d, Ater JL, Copeland DR: Improved neuropsychological outcome in children with brain tumors diagnosed during infancy and treated without cranial irradiation. J Child Neurol 7:281–90, 1992.
11. Evans AE, Jenkin RD, Sposto R, Ortega JA, Wilson CB, Waraw W, Ertel IJ, Kramer S, Chang CH, Leikin SL: The treatment of medulloblastoma: results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg 72:572–82, 1990.
12. Sposto R, Ertel IJ, Jenkin RD, Boesel CP, Venes JL, Ortega JA, Evans AE, Ward W, Hammond D: The effectiveness of chemotherapy for treatment of high-grade astrocytoma in children: results of a randomized trial; a report from the Childrens Cancer Group. J Neuroncol 7:165–77, 1989.
13. Tait DM, Thorton-Jones H, Bloom JL, Lemerle J, Morris-Jones P: Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trials of the International Society of Paediatric Oncology (SIOPI). Eur J Cancer 26:464–69, 1990.
14. Shimada H, Chatten J, Newton WA Jr, Sachs N, Hamoudi AB, Chiba T, Marsden HB, Misugi K: Histopathologic prognostic factors in neuroblastic tumors: definition of subtypes of ganglioneuroblastomas and an age-linked classification of neuroblastomas. J Natl Cancer Inst 73:405–13, 1984.

15. Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY, Hammond D: Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Engl J Med 313:1111–16, 1985.
16. Evans AE, D'Angio GJ, Randolph J: A proposed staging for children with neuroblastoma, Childrens Cancer Group A. Cancer 27:374–78, 1971.
17. Brodeur GM, Pritchard J, Berthold F, Carlson NL, Castel V, Castelberry RP, De Bernardi B, Evans AE, Fanrot M, Hedborg F: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466–77,1993.
18. Matthay KK, Sather HN, Seeger RC, Haase GM, Hammond GD: Excellent outcome of stage II neuroblastoma is independent of residual disease and radiation therapy. J Clin Oncol 7:236–44, 1988.
19. West DC, Shamberger RC, Macklis RM, Kozakewich HP, Wayne AS, Kreissman SG, Korf BR, Lavally B, Grier HE: Stage III neuroblastoma over 1 year of age at diagnosis: improved survival with intensive multimodality therapy including multiple alklylating agents. J Clin Oncol 11:84–90, 1993.

Rate of bicycle-related injuries double for boys

About half of bicycle-related accidents involve head injuries

Boys are twice as likely as girls to be injured while riding their bicycles, possibly because they spend more time riding and perform riskier activities on their bicycles that girls do, according to an article in the April issue of the AMA's *Archives of Pediatrics and Adolescent Medicine.*

Xiaohan Hu, MB, MPH, PhD, from the Hospital for Sick Children and Kiwanis Injury Prevention and Research Program, Toronto, Ontario, Canada, and colleagues compiled their data by conducting telephone surveys of parents with children ages 5–17 who owned a bicycle. They also analyzed hospital discharge records for all children who were admitted to hospitals in the metropolitan Toronto area with bicycle-related injuries from April 1989-March 1991. Complete information on bicycle exposure was received from the parents of 707 children.

The study found that boys had more than double the rate of bicycle-related injuries compared to girls (8.1 and 3.4 per 10,000 population), about half of the injuries suffered were head injuries, and boys were significantly more likely than girls to ride on only one wheel of their bicycle (11.6 vs. 4.0%).

Boys had higher injury rates than girls in every age group. Boys in the 11- to 12-year age group had the highest overall injury rate (10.2 per 10,000 population) and also the highest overall head injury rate (4.8 per 10,000 population). For girls, the injury rate was highest among 9- to 10-year-olds (4.9 per 10,000), however, the highest head injury rate for girls was among 7-8 year olds (2.5 per 10,000).

While more than half of the children in every age group were exposed to bicycling more than 100 hours per year, boys spent more hours and rode longer distances than girls. Boys' riding hours peaked at age 11 or 12, with an average of 228 hours per year. Girls' riding hours peaked at age 9 or 10 with an average of 157 hours per year.

The authors write: "Our finding that boys 11 or 12 years of age had the highest overall and head injury rates per 10,000 persons, while overall injury rates for girls peaked two years earlier, indicated that injuries were more closely associated with exposure time (than distance ridden), as peak hours occurred in the same age groups.

The study found that the median bicycling season for children is from May–October. The average child begins riding a bicycle at 5.5 years and spends a half hour tiding a bicycle on weekdays. On the weekend, the average riding time was two hours for boys and one hour for girls.

The study also found that: "Children's bicycling exposure appears to be inversely associated with parental socioeconomic status. The median riding hours for children whose parents' educational levels were high school or less, college/university, and postgraduate were 184, 154, and 132, respectively; the same pattern was observed when riding hours were analyzed by annual family income."

The authors write: "Bicycle injuries take a significant toll on children. As shown in this study, about 50 percent of hospitalizations were for head injuries, which are largely preventable by wearing a helmet. Other researchers have shown that lack of knowledge of basic bicycling rules, failure to obey traffic regulations, poor bicycle control, and inadequate training were also associated with increased injuries in children. Programs and strategies aimed at correcting these deficiencies should be an integral part of bicycle injury prevention in conjunction with helmet promotion."

Bicycle crashes result in about 600 deaths among children each year in the United States and account for more than 500,000 emergency department visits, according to statistics cited in the study.