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Neuroblastoma

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Introduction

Neuroblastoma is the most common solid tumor of infancy and the most common extracranial solid tumor of childhood. Neuroblastoma is derived from primitive neuroblasts that arise from neural crest cells committed to the development of the sympathetic nervous system and is one of the most enigmatic cancers of childhood. It is known for its heterogeneous clinical presentation and unpredictable behavior, including tumors that regress spontaneously without treatment or progress despite aggressive multi-modal therapy. Our improved understanding of molecular and genetic features of this tumor has shed some light on its diverse clinical behavior.[1] It can be classified into high risk, intermediate risk, and low risk groups based on clinical and biological criteria that can predict prognosis. Although children with low risk neuroblastoma have very good outcomes and excellent long term survival, children with high-risk neuroblastoma continue to do poorly despite significant intensification of conventional treatment. An improved understanding of the molecular biology of neuroblastoma might help us develop targeted therapies that could lead to improved survival and better quality of life for long term survivors.

Epidemiology

Neuroblastoma accounts for approximately 7% of malignancies in children under 15 years of age and approximately 15% of deaths in children due to cancer.[2] It is the most common extracranial solid tumor of childhood and most common malignancy of infancy. Around 2,200 new cases are diagnosed every year in North America and Europe together. About 40% cases are diagnosed in children less than 1 year of age and 90% of cases are diagnosed by 5 years of age. 98% cases are diagnosed by 10 years of age.[3] Rare cases of neuroblastoma do occur in adolescents and adults. There is no difference in disease incidence among different ethnic groups.[3] In the 1980s early detection of neuroblastoma using spot urine catecholamine levels increased early detection but prospective studies did not demonstrate a decrease in mortality.[4, 5] The studies concluded that screening infants under 1 year of age detected an increased number of cases with good prognosis but that screening failed to detect the high risk cases that clinically present at an older age.[6]

Pathology

Neuroblastoma is one of the small round blue cell tumors of childhood and must be differentiated from Ewing's sarcoma, non-Hodgkins lymphoma, peripheral primitive neuroectodermal tumors and undifferentiated soft tissue sarcomas including rhabdomyosarcoma.[1,7] Expression patterns of neurofilament proteins synaptophysin and neuronspecific enolase can be helpful to arrive at the correct diagnosis.

Neuroblastoma comes under the spectrum of peripheral neuroblastic tumors and arises from the progenitor cells of the sympathetic nervous system. In 1984 Shimada and colleagues proposed a classification system for peripheral neuroblastic tumors based on histopathologic features and age to predict clinical behavior. The Shimada system differentiated tumors into favorable or unfavorable histology based on the Schwannian stroma development, grade of neuroblastic differentiation, mitosis-karyorrhexis index (MKI) and age at diagnosis.[8] The Shimada system was further modified to create the international neuroblastoma pathology classification system (INPC). According to the 2003 INPC classification there are 4 morphologic entities. Neuroblastoma is the classical form composed of small uniformly sized cells with dense, hyperchromatic nuclei and scant cytoplasm, with limited to no Schwannian stroma. The Homer-Wright pseudorosette is a classic finding in neuroblastoma. Ganglioneuroma is the fully differentiated benign counterpart of neuroblastoma and is composed of mature ganglion cells, neuropil and Schwann cells. Ganglioneuroblastoma is a heterogeneous mix of neuroblastoma and ganglioneuroma. According to the new classification system, the nodular and intermixed ganglioneuroblastomas are two separate entities, with the nodular form of ganglioneuroblastoma having neuroblastic nodules coexisting with intermixed ganglioneuroblastoma or ganglioneuroma.[9,10] Based on these pathologic features and taking into account the MKI and age of the patient, the INPC assigns a favorable or unfavorable histologic classification to the tumor.

Biological variables

Though the INPC classification based on the Shimada system is a good predictor of outcome, there are several biological variables that correlate with outcome. *MYCN* gene amplification is consistently associated with poor prognosis.[11,12] Similarly, deletion of the short arm of chromosome 1, allelic loss of 11q and gain of 17q are associated with advanced disease and poor prognosis.[13,14] DNA content can be predictive of disease outcome, especially in infants with hyperdiploid tumors, which have a favorable outcome as compared to diploid or near diploid states.[15] High levels of *TrkA* and *TrkC* expression correlate with absence of *MYCN* amplification and good prognosis whereas *TrkB* expression is strongly associated with aggressive tumor behavior and *MYCN* amplification.[16] Many other risk factors have been identified and shown to be associated with neuroblastoma prognosis, and a full understanding of the underlying pathogenesis will likely lead to a comprehensive list of factors prognostic for clinical patient outcome.

Clinical presentation

Neuroblastoma arises from the neural crest cell anywhere along the sympathetic nervous system. Clinical presentation depends on the site of tumor origin and disease extent. Neuroblastoma tumors can be localized or can be metastatic via hematogenous or lymphatic spread.

Most neuroblastoma tumors (65%) arise within the abdomen and approximately half of these arise in the adrenal medulla. The frequency of an adrenal primary site is higher in children than in infants. Infants commonly have tumors along the cervical or thoracic sympathetic chain. Tumors arising in cervical sympathetic chain can present with Horner's syndrome. Tumors in the paraspinal region can extend locally through the neural foramina with compression of the nerve roots and symptoms of cord compression. Tumors arising in the organ of Zukerkandl may present with bowel and bladder obstruction. Vascular obstruction can result in superior vena cava syndrome for cervical tumors or swelling of the scrotum and lower extremities for pelvic tumors.[1]

Neuroblastoma is frequently associated with paraneoplastic syndromes such as opsoclonus-myoclonus-ataxia syndrome with myoclonic jerking and random jerking eye movements with or without cerebellar ataxia, and Kerner Morrison syndrome with secretary diarrhea due to tumor cell secretion of vasoactive intestinal peptide. Patients with paraneoplastic syndromes tend to have a more favorable prognosis.[6,17]

Metastatic neuroblastoma at presentation is seen in approximately 50% of the patients. Common sites of metastasis include lymph nodes, bones, bone marrow and liver. Bony metastases can be associated with a limp or extremity pain, and the "raccoon eyes" often seen in a child with neuroblastoma is the result of tumor involvement of the orbital bones. Bone marrow involvement can be associated with cytopenias. Rarely the patient will present with renin-mediated hypertension due to compression of renal vasculature.

A unique clinical presentation of neuroblastoma occurs in infants with metastatic disease in a particular pattern, termed stage 4S. Infants with stage 4S disease occurs in 5% of the patients with localized primary tumors and dissemination limited to skin, bone marrow and liver, without cortical bone involvement. These stage 4S tumors can regress spontaneously without therapy and are associated with a very good prognosis.[1,6]

Diagnosis

The diagnosis of neuroblastoma is initially suspected when a child presents with a mass lesion or with one of the classical paraneoplastic syndromes. An increasing number of tumors are being detected during prenatal ultrasonography. A full evaluation for neuroblastoma includes imaging of the primary tumor and an evaluation for metastatic disease. CT scans of the neck, chest, abdomen and/or pelvis are often the initial diagnostic tests to delineate tumor extent and metastasis. MRI is superior for evaluation of paraspinal tumors that present with symptoms of radiculopathy or cord compression. Pathology is essential to confirm the diagnosis of neuroblastoma. Definitive pathology from the primary lesion or the identification of small round blue tumor cells from the bone marrow with an elevation in the urinary levels of catecholamines are sufficient to confirm the diagnosis of neuroblastoma. Initial surgery should gather adequate specimens for histologic and molecular testing to help assess the known prognostic factors. Bone marrow aspiration with biopsy should be performed in all patients. Cortical bone involvement is assessed by bone scan. The compound meta-iodobenzylguanidine (MIBG) is actively transported into the neuroblastoma cell by the norepinephrine transporter, and scans using MIBG labeled with either ^{123}I or ^{131}I can be used for an overall assessment of disease spread. However, MIBG scans can be negative in up to 10% of cases. The role of PET scans in children with neuroblastoma is unknown but is currently under investigation.[18]

The Staging system

Until 1988 there was no consensus among various international oncology groups on the criteria for staging of children with neuroblastoma. The International Neuroblastoma Staging System (INSS) was established by a consensus statement from pediatric oncology cooperative groups in the U.S., Europe and Japan (Table 1).

Risk stratification

Clinical heterogeneity is a hallmark of neuroblastoma. Based on stage, age, *MYCN* amplification and Shimada histology, the COG stratifies patients into low risk, intermediate risk, and high risk groups and assigns treatments according to these risk groups. Treatment algorithms are continuously evolving as we develop a better understanding of the molecular biology of neuroblastoma. Table 2 shows the current risk stratification used by Children's Oncology Group. As new molecular markers that predict outcome and responses to therapy are identified, further refinements to the risk grouping will need to be performed and validated.

Table 1. INSS surgical staging

Stage 1

Localized tumor with complete gross excision with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)

Stage 2A

Localized tumor with incomplete gross resection; representative ipsilateral non-adherent lymph nodes negative for tumor microscopically

Stage 2B

Localized tumor with or without complete gross resection, with ipsilateral non adherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically

Stage 3

Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement

Stage 4

Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)

Stage 4S

Localize primary tumor (as defined in stage 1, 2A or 2B) in infants less than 12 months of age with dissemination limited to skin, liver, and/or bone marrow (<10% malignant cells)

Principles of therapy

The treatment of neuroblastoma often involves surgery, chemotherapy, biologic agents and radiation as well as observation in special circumstances. The role of each modality is determined by the expected behavior of the individual tumor considering clinical and biological variables.

Table 2. Children's Oncology Group Risk stratification

Risk group	Stage	Age	MYCN amplification status	Ploidy	Shimada
Low risk	1	Any	Any	Any	Any
Low risk	2a/2b	Any	Not amplified	Any	Any
High risk	2a/2b	Any	Amplified	Any	Any
Intermediate risk	3	<547days	Not amplified	Any	Any
Intermediate risk	3	>547days	Not amplified	Any	FH
High risk	3	Any	Amplified	Any	Any
High risk	3	>547days	Not amplified	Any	UH
High risk	4	<365days	Amplified	Any	Any
Intermediate risk	4	<365days	Not amplified	Any	Any
High risk	4	365 to <547 days	Amplified	Any	Any

High risk	4	365 to <547 days	Any	DI = 1	Any
High risk	4	365 to <547 days	Any	Any	UH
Intermediate risk	4	365 to < 547 days	Not amplified	DI > 1	FH
High risk	4	>547 days	Any	Any	Any
Low risk	4S	<365 days	Not amplified	DI > 1	FH
Intermediate risk	4S	<365 days	Not amplified	DI = 1	Any
Intermediate risk	4S	<365 days	Not amplified	Any	UH
High risk 4S	<365 days		Amplified	Any	Any

Surgery

Surgery plays a pivotal role in the diagnosis and treatment of neuroblastoma. The overall goal of surgery is to establish the diagnosis, provide tissue for evaluation of biological markers, stage the disease according to the INSS criteria (Table 1) and attempt to totally excise the primary tumor if feasible without damaging adjacent vital organs and vital structures. If the primary tumor is considered unresectable, an adequate biopsy should be obtained and chemotherapy or other treatment instituted as needed. A fine needle aspiration rarely provides adequate diagnostic information and should be avoided.

For stage 4S tumors, surgical resection is no longer required in most cases, but a biopsy should be performed for assessment of biological variables. Image defined risk factors as recently defined by the International Neuroblastoma Risk Group (INRG) criteria will be employed in the future for the surgeon to determine pre-surgical risks (Table 3).[19] After initial therapy, additional surgery may be performed to achieve complete or near complete resection. In patients with epidural tumors who present with cord compression, chemotherapy is considered the primary modality of treatment. Laminectomy should be avoided if possible.

Table 3. INRG Image Defined Risk Factors

Neck
1. Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
2. Tumor extending to base of skull
3. Tumor compressing the trachea

Cervicothoracic junction
1. Tumor encasing brachial plexus roots
2. Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
3. Tumor compressing the trachea

Thorax
1. Tumor encasing the aorta and/or major branches
2. Tumor compressing the trachea or principal bronchi
3. Lower left mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12

Thoraco-abdominal
1. Tumor encasing the aorta and/or vena cava

Abdomen
1. Tumor infiltrating the porta hepatic and/or the hepatoduodenal ligament
2. Tumor encasing branches of the superior mesenteric artery at the mesenteric root
3. Tumor encasing the origin of the celiac axis, and/or of the superior mesenteric artery
4. Tumor invading one or both renal pedicles
5. Tumor encasing the aorta and/or vena cava
6. Tumor encasing the iliac vessels
7. Pelvic tumor crossing the sciatic notch

Dumbbell tumors with symptoms of spinal cord compression
1. Whatever the localization

Infiltration of adjacent organs or structures
1. Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

Chemotherapy

Chemotherapy is the principal modality of treatment for intermediate and high risk neuroblastoma. Symptomatic patients with low risk neuroblastoma involving vital organs also receive chemotherapy. Carboplatin, cisplatin, vincristine, cyclophosphamide, doxorubicin, topotecan, ifosfamide, and etoposide are the commonly used first line drugs for neuroblastoma. To minimize exposure and the long-term late effects of chemotherapy, risk based chemotherapy regimens are employed by different pediatric oncology groups as detailed below.

Radiation

Neuroblastoma is a radiosensitive tumor, and radiation therapy has been an important modality for the treatment of neuroblastoma. However, the role of radiation in modern management of neuroblastoma is limited because of its long term sequelae. Radiation is generally utilized for patients with high-risk neuroblastoma and in cases of relapsed disease for palliative symptom control. Localized radiation therapy can also be delivered through radiolabelled MIBG in tumors found to be avid for MIBG. Alternatively, antibodies to proteins and glycoproteins expressed on neuroblastoma tumor cells can be labeled with radioactive isotopes and used to deliver radiotherapy specifically to neuroblastoma tumor cells. Several studies have demonstrated the efficacy of radiolabelled MIBG, and current studies are pursuing the optimal role of ^{131}I-MIBG in the management of neuroblastoma.[20]

Treatment of low risk Neuroblastoma

Long-term survival rates for children with low risk neuroblastoma are generally over 90% with current treatment. Maximal tumor resection is recommended for localized tumors with favorable biologic characteristics. Chemotherapy is generally not required for incompletely resected tumors with favorable characteristics, but can be utilized for patients with life-or organ-threatening symptoms or for patients who have recurrences or progressive disease. Recurrences are most commonly local and can be managed with surgery or additional therapy with radiation or chemotherapy. Metastatic recurrences are rare but often are salvageable with chemotherapy.[21,22]

Intraspinal neuroblastoma with spinal cord compression is managed with chemotherapy alone. Surgery is employed only if there is no response to chemotherapy.[23] The majority of patients with stage 4S neuroblastoma fall into the low risk group and can be observed without any treatment, although treatment with surgery, radiation, or chemotherapy may be required for an acutely ill child.

Treatment of intermediate risk neuroblastoma

Current treatment for children with intermediate risk neuroblastoma involves surgery and moderate chemotherapy. A recently completed Children's Oncology Group protocol included selected patients with INSS stage 3 or 4 neuroblastoma with non-amplified *MYCN* who were classified with either favorable and unfavorable biological features based on age at diagnosis, DNA index and Shimada histology. Using a combination of carboplatin, etoposide, cyclophosphamide and doxorubicin, 3 year event-free survival rates were reported as >90%,[24] demonstrating that good outcomes could be maintained with treatment reduction for patients identified with lower risk features. Based on these encouraging results the current Children's Oncology Group study is evaluating the roles of LOH at 1p and 11q as additional prognostic features to further refine therapy.

Treatment of high risk neuroblastoma

Children with high-risk neuroblastoma have a poor prognosis despite aggressive therapy. Current treatment strategies utilize induction with high dose chemotherapy to reduce tumor burden, followed by surgical resection of the primary tumor. Further consolidation treatment often includes myeloablative chemotherapy followed by autologous stem cell rescue and focal radiation therapy. Subsequent maintenance therapy with differentiation agents such as 13-*cis*-retinoic acid is employed to eradicate minimal residual disease. Even with this aggressive therapy, the long-term overall survival rates of children with high-risk neuroblastoma remain around 30% under current treatment protocols.[25] Various strategies are being implemented to improve the outcome of this group of patients. Recent trials have investigated the efficacy of using purged compared to unpurged bone marrow for stem cell rescue on treatment outcomes, in addition to trials using passive immunotherapy with monoclonal antibodies against the neuroblastoma tumor cell marker GD2 after stem cell rescue.

Treatment of relapsed and refractory neuroblastoma

Treatment of relapsed neuroblastoma poses a challenge, particularly for patients with high-risk and refractory disease. There are multiple experimental approaches for the treatment of relapsed or refractory neuroblastoma that are currently being tested in a variety of national and international settings. With recent developments in our understanding of the molecular biology of neuroblastoma, a wide range of new agents are undergoing preclinical and clinical evaluations. A significant number of novel agents are currently under investigation in early phase clinical trials for children with neuroblastoma, leading to the hope that improved outcomes with reduced long-term side effects will be achievable soon (Table 4).[26]

Table 4.[26] Novel therapeutic agents currently in employed in clinical trials for treatment of neuroblastoma

Investigational agents	Class of agent
ABT - 751	Anti mitotic agent
Temsirolimus	mTOR inhibitor
IMC-A12	IGF1 receptor antibody
Beta-glucan	Adjuvant to anti-GD2 anti body therapy
BSO/melphalan	Chemosensitizer with stem cell transplant
Fenretinide	Retinoid
CEP-701	TrkB inhibitor
Nifurtimox	Antiparasitic agent
Bortezomib	Proteosome inhibitor
Bevacizumab	Anti-VEGF receptor antibody
Zactima	VEGFR + EGFR inhibitor
MLN8237	Aurora kinase inhibitor
^{90}Y-DOTA-try3-octreotide	Radiopharmaceutical

Future considerations

Significant improvements have been made over the last few decades in the treatment of children with neuroblastoma, particularly in children with low and intermediate risk disease. Current trials continue to refine risk stratification based on newer biological variables, to continue the attempts to define the minimal therapy needed to maintain excellent outcomes and minimize long term side effects. However, even with aggressive treatment regimens, the overall survival for children with high-risk neuroblastoma remains poor, and newer agents hold promise for improved survival in children with high-risk neuroblastoma.

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