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Neuroblastoma: Clinical and Biological Approach to Risk Stratification and Treatment

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Abstract

Neuroblastoma is the most common extra-cranial solid tumors of childhood and the most common in the first year of life. It is a unique malignancy in that infants often present with either localized or metastatic disease that can spontaneously regress without intervention while older children can succumb to the disease after months to years of arduous therapy. Given this wide range of outcomes, the International Neuroblastoma Risk Group was created to stratify patients based on presenting characteristics and tumor biology in order to guide intensity of treatment strategies. The goal has been to decrease therapy for low risk patients to avoid long-term complications while augmenting and targeting therapies for high risk patients to improve overall survival. The international risk stratification depends on age, stage, histology, *MYCN* gene amplification status, tumor cell ploidy and segmental chromosomal abnormalities. Treatment for asymptomatic low risk patients with an estimated survival of >98% is often observation or surgical resection alone, whereas intermediate risk patients, with an estimated survival of >90% require moderate doses of response-adjusted chemotherapy along with resection. High risk patients undergo multiple cycles of combination chemotherapy before surgery, followed by consolidation with myeloablative autologous hematopoietic stem cell transplantation and local radiation, and finally immunotherapy with differentiation therapy as maintenance phase. With this approach, outcome for patients with neuroblastoma has improved, as the field continues to expand efforts in more targeted therapies for high risk patients.

Keywords

Neuroblastoma; Pediatric Oncology; Clinical Presentation; Treatment; Risk Classification

Introduction

Neuroblastoma is the most common extracranial solid tumor of childhood (Maris, 2010). It arises from the developing sympathetic nervous system from neural crest cells, usually resulting in tumors in the adrenal glands or the sympathetic ganglia (Irwin and Park, 2015). The age-standardized annual incidence in North America is 5.5 to 11.5 cases per million people (Stiller and Parkin, 1992). It is the most common malignancy overall in the first year

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of life with a median age at diagnosis of 18 months and 90% of cases diagnosed by 10 years of age (London, et al., 2005).

The clinical presentation can be quite heterogeneous, ranging from asymptomatic incidental tumors to widespread metastases with systemic manifestations. The clinical and biological heterogeneity leads to differences in outcome, ranging from spontaneous regression to inexorable progression, metastasis and death despite intensive therapy (Matthay, et al., 2016). In addition to the usual prognostic importance of disease stage, many biologic factors help to explain the clinical behavior in neuroblastoma, including histologic features, cytogenetic features, and the molecular changes, particularly amplification of the *MYCN* oncogene (Brodeur, et al., 1984, Seeger, et al., 1985). The better understanding of the prognostic importance and role of these clinical and biologic features has allowed for more precise risk stratification to guide therapy, in order to improve outcome for high risk patients by intensification of treatment and addition of novel agents while decreasing doses of chemotherapy for lower risk patients to reduce late effects. Recent advances of molecular changes involved in tumor initiation and progression have led to early phase clinical trials to test new inhibitors of potential tumor and tumor microenvironment targets.

This review will focus on the clinical aspects of this disease: the clinical presentation, diagnosis, risk stratification, and therapy for children with neuroblastoma.

Clinical Presentation

Clinical presentation of neuroblastoma varies widely by age and stage. The location of the primary tumor and any metastatic sites dictates the symptomatology. Neuroblastoma arises from the sympathetic nervous system, most often from the adrenal medulla (Vo, et al., 2014). The remainder arise from the paraspinal or other sympathetic ganglia and can present anywhere from the neck to the pelvis.

Neuroblastoma is prone to involve surrounding nerve roots due to the paraspinal location of most of the sympathetic ganglia; thus, tumors arising in the neck frequently cause Horner syndrome. Thoracic tumors usually present in the posterior mediastinum and paraspinal ganglia, frequently with invasion of the neural foramina. A localized abdominal or pelvic masses can be noted by the caregivers without any symptoms or can cause significant distention with or without pain. Pelvic tumors can also cause neurologic symptoms such as bladder dysfunction, constipation, or lower extremity pain or weakness due to nerve root involvement. Any of these locations has the potential to invade the neural foramina and cause spinal cord compression symptoms.

Metastases are present at diagnosis in about 50% of patients, with the bone marrow, bone and regional lymph nodes being the most common sites while involvement of central nervous system and lungs are rare, present in less than 5% of metastatic patients at diagnosis (DuBois, et al., 1999, Morgenstern, et al., 2016). Extensive liver involvement can be seen in infants and can cause liver disease such as a coagulopathy, and renal and lung dysfunction due to abdominal distention. Also more common in infants, metastases in the skin can appear as painless subcutaneous nodules anywhere on the body with a blue hue (Figure 1).

Bone marrow infiltration, present in 80% of metastatic patients, can cause anemia and thrombocytopenia. Metastases to the bone can be very painful causing limping or refusal to bear weight. Bone lesions are commonly seen in the skull, and if they are in the periorbital region, cause proptosis or periorbital bruising (known commonly as “raccoon eyes” or Hutchinson syndrome).

Neuroblastoma can also present with systemic symptoms such as fever or weight loss. Neuroblastomas can release catecholamines with patients experiencing flushing, tachycardia or hypertension. In a very rare paraneoplastic phenomenon, the tumor can secrete vasoactive intestinal peptide (VIP), which causes profuse watery diarrhea. Paraneoplastic presentation is also possible with opsoclonus myoclonus syndrome (OMS), in which patients can have an array of neurologic symptoms including opsoclonus which is spontaneous saccades of the eyes in all directions, myoclonus (involuntary muscle twitching), and occasionally ataxia or other cerebellar signs. A child that presents with this constellation of symptoms, even without overt signs of malignancy, should be evaluated for neuroblastoma, as it has been diagnosed in 50–80% of patients with OMS, but only 2–3% of children with neuroblastoma overall are affected by OMS (Hero and Schleiermacher, 2013). The neurologic symptoms are probably attributable to anti-neuronal antibodies cross-reacting with cerebellum (Antunes, et al., 2000, Rudnick, et al., 2001).

Evaluation, Staging and Screening

When neuroblastoma is suspected, a variety of laboratory tests, imaging studies and pathologic examinations are required to confirm the diagnosis and staging. Initially a complete blood count, prothrombin time and partial thromboplastin time, uric acid, electrolytes, creatinine, liver function tests, ferritin and lactate dehydrogenase should be tested; the latter two tests indicate a lower survival when elevated (Cohn, et al., 2009, Hann, et al., 1985, Hann, et al., 1980, Shuster, et al., 1992). Urine should also be collected for vanillylmandelic acid (VMA), homovanillic acid (HVA) and dopamine levels. These catecholamines and catecholamine metabolites are found in 90% of children with neuroblastoma. Plasma-free and total normetadrenaline, metadrenaline and methoxytyramine can be drawn in the serum as a replacement if urine cannot be collected from a young child (Franscini, et al., 2015). Bilateral bone marrow biopsies may be used to confirm the diagnosis if tumor is seen and urine catecholamines are elevated, and these are also required to complete staging, with immunohistochemistry to increase sensitivity of tumor detection (Beiske, et al., 2009).

Extensive imaging is required for staging, tumor characterization and surgical planning. Ultrasound is an accessible way without requiring sedation to confirm the presence and location of a mass. However, cross sectional imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) is necessary for accurate localization and characterization (Figure 2A). The primary site should be included as well as the chest, abdomen and pelvis to check for lymph node spread or further extension. MRI is preferred if possible as it does not use ionizing radiation and can provide superior imaging, especially of the spinal cord, but has the disadvantage of more often requiring sedation in young children. For neuroblastoma, an ^{123}I-metaiodobenzylguanidine (MIBG) scan is essential for staging

and evaluation of response (Figure 2B) (Matthay, et al., 2010). MIBG is a radiolabeled molecule similar in structure to norepinephrine, that is taken up by the norepinephrine transporter in 90% of neuroblastomas (Dubois, et al., 2012). Thus, an MIBG scan provides an extremely specific method of discovering and following sites of metastases, which is more specific and sensitive than technetium bone scan (Gauguet, et al., 2017). MIBG can be combined with other imaging modalities such as is done in a single-photon emission computed tomography (SPECT) to provide more exact anatomical localization of the MIBG uptake (Figure 2C) (Biermann, et al., 2013). Multiple semi-quantitative scoring systems for MIBG uptake in neuroblastoma exist to track metastatic disease burden and have been shown to be associated with prognosis (Decarolis, et al., 2013, Yanik, et al., 2013). In the 10% of neuroblastomas that are MIBG non-avid, or if MIBG is not available, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) CT is an acceptable alternative (Sharp, et al., 2009). Newer radiologic techniques are also under investigation for utility in neuroblastoma such as ^{18}F-l-dihydroxyphenylalanine-PET (18F-DOPA-PET) and gallium-68 (^{68}Ga)-DOTATATE-PET (Gains, et al., 2011, Liu, et al., 2016).

Biopsy of the tumor confirms the diagnosis and provides important information on prognosis. Neuroblastoma is a small round blue cell tumor that can be differentiated from other tumors such as Ewing sarcoma and other sarcomas, lymphoma, and Wilms tumor by the appropriate immunohistochemical stains (Hachitanda, et al., 1989, Miettinen, 1987). These tumors can show differing levels of maturation. Neuroblastoma is primarily immature while a ganglioneuroma is composed of cells that have matured and completed differentiation as ganglion cells. A ganglioneuroblastoma has components of both of these types of tumors. The International Neuroblastoma Pathology Committee further subtyped these immunohistochemical classifications by the amount of Schwannian stroma present in the tumor (Shimada, et al., 1999, Shimada, et al., 2001). These subtypes are neuroblastoma which is Schwannian stroma-poor, ganglioneuroblastoma intermixed which is Schwannian stroma-rich, ganglioneuroblastoma nodular which is a combination of Schwannian stroma-rich and poor, and ganglioneuroma which is Schwannian stroma-dominant. Ganglioneuroblastoma nodular is divided into favorable and unfavorable, depending on the mitosis-karyorrexis index (MKI) and patient age (Peuchmaur, et al., 2003). Generally, poorly differentiated or undifferentiated histology portend a worse prognosis, but age is also an important indicator. In an infant <18 months, a poorly differentiated neuroblastoma is still considered favorable if the MKI is not high, but in a patient >18 months, a poorly differentiated neuroblastoma is always unfavorable (Shimada, et al., 1999). In the same International Neuroblastoma Pathology Classification, a child >5 years of age with neuroblastoma is always considered unfavorable, but ganglioneuroblastoma can still be considered favorable.

Molecular testing of the tumor has become increasingly important as well to determine overall prognosis. *MYCN* gene amplification is one of the most important markers of aggressive disease and poor prognosis in neuroblastoma (Bagatell, et al., 2009, Brodeur, et al., 1984, Campbell, et al., 2017, Seeger, et al., 1985). *MYCN* amplification is most commonly measured by fluorescent *in situ* hybridization (FISH) as a fourfold increase in the *MYCN* signal number compared with the reference probe located on chromosome 2q (Ambros, et al., 2009). Cell ploidy is also an important prognostic marker in neuroblastoma

with triploidy or hyperdiploidy having a better prognosis than diploidy (Ambros, et al., 2009). This is measured by flow cytometry and reports a DNA index of 1 for diploidy, thus a value greater than 1 is associated with better outcome. Segmental chromosomal copy number alterations are also seen in neuroblastoma and are commonly measured by array comparative genomic hybridization. The most common of these are gain of 17q, loss of 1p and loss of 11q, with multiple other segmental chromosomal alterations that are less common, but all are associated with worse outcome (Attiyeh, et al., 2005, Bown, et al., 1999, Schleiermacher, et al., 2012).

Mutations in specific genes in neuroblastoma are not common but the presence of these alterations are being discovered at an increasing rate with the next generation sequencing becoming more accessible (Molenaar, et al., 2012, Pugh, et al., 2013). One such mutation that was discovered in the germline DNA in families with heritable neuroblastoma is in the *ALK* gene, which has since also been shown to be somatically mutated spontaneously in a subset of neuroblastomas (Chen, et al., 2008, George, et al., 2008, Janoueix-Lerosey, et al., 2008, Mosse, et al., 2008). Familial neuroblastoma is rare, found in approximately 1% of patients, but *ALK* germline testing should be considered in this context. Tumor testing should also be considered in newly diagnosed non-heritable cases, where 8–15% of patients are estimated to have somatic mutations in ALK, as there are emerging therapies targeting this constitutively active kinase (Mosse, et al., 2013). *PHOX2B* germline mutations are another cause for familial neuroblastoma but have not been found commonly as a somatic mutation (Trochet, et al., 2004). It has also been observed that germline mutations in other cancer associated genes such as *TP53*, *NF1*, *BRCA1/2*, *NRAS*, *APC* and *PTPN11* can predispose to neuroblastoma as well. Somatic mutations are not common in neuroblastoma but have been seen repeatedly in a few genes such as loss of function alterations in *ATRX* (which is more common in adolescents) (Cheung, et al., 2012, Molenaar, et al., 2012, Pugh, et al., 2013) and promoter rearrangements in *TERT* (Peifer, et al., 2015). Both of these alterations have been shown to elongate telomeres, which is a known mechanism of survival in cancer cells.

Given that metastatic neuroblastoma can be quite advanced at diagnosis, attempts to screen for this disease in infants were undertaken. Urine catecholamines are rather sensitive and specific so they were used for screening trials across the world. In Japan, mass screening led to possible over-diagnosis of neuroblastoma, but overall mortality was lower in the screened group (Hisashige and Group, 2014, Hiyama, et al., 2008, Sawada, et al., 1982, Yamamoto, et al., 1995). The neuroblastomas discovered by screening, however, tended to have more favorable molecular characteristics (Nakagawara, et al., 1991), and when screening was terminated, Japan did not see an increase in mortality from neuroblastoma (Kerbl, et al., 2003, Shinagawa, et al., 2017). Screening in North America showed similar results (Woods, et al., 2002). A large German study also showed an over-diagnosis of low risk patients and no improvement in the detection or mortality of high risk patients even when screening was performed at 12 months of age instead of in the first 3 months (Schilling, et al., 2002, Schilling, et al., 2003). In aggregate, screening studies for neuroblastoma did not decrease mortality and likely led to over-diagnosis of patients who did not benefit from earlier intervention, so wide-spread screening has not been implemented.

Risk Stratification

Prior to the formation of the International Neuroblastoma Risk Group (INRG) Task Force, multiple staging systems were used across the world, making research difficult to perform and compare. The most recent and frequently used was the International Neuroblastoma Staging System (INSS), used from about 1989–2010, was based, in part, on the extent of surgical resection (Brodeur, et al., 1993). This was problematic as it did not allow for pretreatment classification of stage, making comparison across clinical groups, especially for research purposes, more complex and not well standardized.

In 2009, the INRG Task Force published their recommendations both for new staging and risk group stratification (Table 1 and Figure 3) (Cohn, et al., 2009, Monclair, et al., 2009). INRG staging is based on image-defined risk factors (IDRFs) pre-therapy rather than post-surgical. These IDRFs were chosen based on elements that represent that that the tumor is more threatening to the patient or could make surgical resection more dangerous, thus less successful. IDRFs include: tumor extension into a second body compartment, encasement of any large blood vessels, tracheal or large bronchial compression, involvement of major nerve roots (such as the brachial plexus), invasion of the spinal canal, or infiltration of the nearby kidneys, mesentery, pericardium, liver, diaphragm or pancreas. These are predictive of worse event-free and overall survival.

There are four INRG stages (Table 1): L1, L2, M and MS (Monclair, et al., 2009). L1 is local disease only, not meeting criteria for any of the IDRFs. L2 is locoregional tumors with one or more IDRFs. Local lymph node status is not included in the new INRG staging. M encompasses all patients with metastatic disease, except for MS. MS is analogous to the old stage 4S and includes metastatic tumor in children less than 18 months of age that is restricted to the liver, skin and/or bone marrow. INSS stage 4S only included infants less than 12 months, but data showing excellent outcome in these patients with the same metastatic pattern out to 18 months, providing their tumor biology was favorable (Taggart, et al., 2011), led to the increase in this age limit. Furthermore, the MS stage does not exclude patients with large unresectable primary tumors, unlike INSS 4S, where the primary tumor must be only stage 1 or 2. With the complex nature of risk factors influencing outcome in patients with neuroblastoma, however, treatment decisions cannot be based solely on these staging criteria, but further pathologic and molecular risk stratification is necessary to assign therapy in this heterogeneous disease.

The INRG Task Force then derived these risk stratifications including not only stage, but tumor biology (Cohn, et al., 2009). They collected data from over 8000 patients from cooperative groups in North America, Europe and Japan. When available, they explored 35 different potential risk factors and compared these to event-free and overall survival. They made Kaplan-Meier survival curves for the condensed risk factors and assessed which were most significantly associated with outcome in order to make survival trees with branch points that could form prognostic categories. Using the risk factors that were the most significant as well as clinically relevant, they chose INRG staging, age, histologic category, grade of tumor differentiation, *MYCN* amplification, 11q aberration and ploidy to divide patients into pretreatment risk groups (see Figure 3). Generally speaking, poorly

differentiated or undifferentiated, *MYCN* amplified, presences of 11q aberration and diploid are considered unfavorable biologic characteristics. Very low risk is defined as an event-free survival of >85%, low risk is 75–85%, intermediate risk is 50–75% and high risk is <50%.

These risk stratifications help in understanding the amount that each risk factor contributes to survival in a way that separate survival curves cannot. For example, in a patient with MS disease that is *MYCN* non-amplified, the presence of an 11q aberration would increase them from very low risk to high risk, whereas with other stages of disease, it does not have such a dramatic effect on outcome. This system is complex but allows for very specific homogenous grouping of patients with neuroblastoma, and simplifies how researchers and clinicians alike can communicate about patients and consider the intensity of therapy needed. Event-free survival curves from Children's Oncology Group (COG) studies by these risk groups are shown in Figure 4 (Park, et al., 2013).

Current Treatment Regimens

In the low and intermediate risk patients, high overall survival of greater than 90% has been achieved while minimizing therapy (Baker, et al., 2010, Rubie, et al., 2011, Strother, et al., 2012). While significant progress has been made in high risk patients, the long-term survival is still below 50%, so the focus has been on intensifying treatment and complementing standard chemotherapy with targeted therapies. A patient with newly diagnosed neuroblastoma can be treated with a wide range of therapies including observation only, surgery, chemotherapy, radiation, immunotherapy, differentiation therapy and autologous stem cell transplant. The INRG classification has been valuable in better understanding prognosis and thus guiding systematic therapy decisions suggested by the international cooperative groups, mainly the Children's Oncology Group (COG) and the International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) (Figure 5).

The mainstay of treatment for low risk L1/L2 patients has been complete surgical resection if possible. More recently, however, observation alone, even without a biopsy to confirm the diagnosis, has been shown to be an appropriate approach in infants less than six months of age with an adrenal tumor less than 16 ml in volume without symptoms, as reported in a COG pilot study (Nuchtern, et al., 2012). Observation is appropriate, as a large proportion of these tumors will spontaneously regression without therapy, and surgical complications are not insignificant in these young patients. Recommended monitoring initially is every six weeks, with physical exams, imaging (MRI or ultrasound) and urine catecholamines. After observing for rapid tumor growth for the first 12 weeks, recommended monitoring can be spaced to every three months for the first year, then every six months. Repeating the metastatic evaluation in these cases is not necessary unless there is evidence of local tumor progression (Nuchtern, et al., 2012). Studies are ongoing in the COG (ClinicalTrials.gov Identifier NCT02176967) to assess if these recommendations can be expanded to infants up to 12 months with L1 tumors, including non-adrenal tumors if urine catecholamines are elevated or MIBG uptake demonstrated. Generally, the other infants who have INRG very low or low risk disease are eligible for a trial of observation after biopsy confirms favorable histologic and molecular subtypes, including *MYCN* non-amplification, if the patient has no symptoms related to their tumor or concerning IDRFs, but confirmatory studies are ongoing

(De Bernardi, et al., 2009, Hero, et al., 2008, Rubie, et al., 2011, Strother, et al., 2012). If, however, there are symptoms, problematic IDRFs or the patients are older than 12 months, either surgical resection or limited chemotherapy to decrease tumor burden is recommended. While gross total resection is preferable, localized L2 tumors with favorable histology and molecular findings can be safely observed even if not completely removed (Iehara, et al., 2013, Marachelian, et al., 2012, Strother, et al., 2012).

For low risk MS patients, if they are asymptomatic and have favorable biology (*MYCN* non-amplified, no 11q aberration and hyperdiploid), observation is also appropriate without surgery or chemotherapy, given the excellent survival and frequent spontaneous regression (Strother, et al., 2012, Taggart, et al., 2011). The exceptions are those infants in the first few months of life with massive hepatomegaly, who require emergent chemotherapy to avoid life-threatening consequences of respiratory impairment or abdominal compression syndrome (Nickerson, et al., 2000). Stage MS patients with unfavorable biologic features, such as diploidy or segmental chromosome abnormalities also require chemotherapy, while those with *MYCN* gene amplification should be treated as high risk (Taggart, et al., 2011).

For intermediate risk neuroblastoma, treatment can vary depending on individual response to therapy. This intermediate group is largely comprised of L2 tumors that are not *MYCN* amplified but are either histologically or genetically unfavorable (either undifferentiated or presence of 11q aberration), stage M disease in patients less than 18 months, and stage MS with unfavorable biology. Usually patients are treated with two to eight cycles of chemotherapy, depending on response to treatment. This chemotherapy may be given in an outpatient setting and is less dose intensive than that prescribed to the high risk patients. Surgery to remove the primary tumor is indicated when possible, but as in the low risk patients, complete resection is not essential (Baker, et al., 2010, Defferrari, et al., 2015, Kohler, et al., 2013, Marachelian, et al., 2012). However, the patients over 18 months with L2 tumors that cannot be resected have a lower overall survival, thus more intense therapy including radiation therapy for local control is recommended (Baker, et al., 2010, Defferrari, et al., 2015, Kohler, et al., 2013, Matthay, et al., 1998).

High risk disease has overall poor long-term outcome, despite the improvement over the past two decades from 29% to 50% 5-year survival (Pinto, et al., 2015). Therefore, the focus has been on continually increasing therapy intensity, with a resulting prolonged and intensive course for patients and families, with significant in-patient hospital stays (see Figure 5). The high risk patients include stage M with age greater than 18 months at diagnosis and patients with any age and stage with *MYCN* amplification. L2 patients with unfavorable histology and age greater than 18 months are often included in the high risk group as well, though the benefit of myeloablative therapy in this subgroup has not been unequivocally demonstrated (Meany, et al., 2014, Park, et al., 2009). Treatment starts with multiple cycles of induction chemotherapy to reduce tumor burden, making it more amenable to surgical resection. Surgery is then done to remove the primary tumor. This is followed by one or two courses of myeloablative therapy with autologous stem cell transplantation, then radiation to the primary tumor bed. Maintenance therapy is comprised of differentiation therapy with isotretinoin and immunotherapy with anti-GD2 monoclonal antibody and cytokines. Treatment duration is approximately 18 months or longer if there are delays.

The purpose of induction chemotherapy, which typically includes a platinum drug, anthracyclines, and alkylating agents, is to decrease tumor burden, eliminate metastatic deposits, and to allow for safer surgical removal of the primary tumor. The primary tumor often encases important blood vessels, such as the aorta or renal arteries, or invade neural foramina, making complete surgical resection dangerous or impossible at presentation. Patients with complete or very good partial response to induction, which, have a significantly improved event free survival than those who responded less robustly, meaning that response to induction is an important prognostic indicator (Ladenstein, et al., 1998, Matthay, et al., 1999, Yanik, et al., 2015, Yanik, et al., 2017, Yanik, et al., 2013). In practice, if a patient has not had a complete response, other therapies, such as additional chemotherapy with or without immunotherapy (Modak, et al., 2017), or radiopharmaceutical therapy with ^{131}I-MIBG (Matthay, et al., 2007), are often utilized to attempt to achieve complete response before stem cell transplantation. In North America, common regimens used to improve metastatic response include immunochemotherapy (Mody, et al., 2017), ^{131}I-MIBG therapy (Matthay, et al., 2007), or simply irinotecan with temozolomide (Bagatell, et al., 2011). The International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) group in their current high risk protocol add a combination of topotecan, vincristine, and doxorubicin to try to achieve metastatic response (Amoroso, et al., 2017), and previously used a protocol combining ^{131}I-MIBG with topotecan (Gaze, et al., 2005).

The INRG recently published new guidelines on measuring treatment response which remains based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, but includes semi-quantitative scoring criteria for MIBG scans (Matthay, et al., 2010) as well as evaluation of percent tumor in bone marrow biopsies (Burchill, et al., 2017, Park, et al., 2017).

Surgical resection is typically scheduled for the end or near the end of induction chemotherapy and removes the remaining primary tumor. If it is safe, complete resection should be attempted. However, in patients with metastatic disease, it has not yet been proven to be beneficial to overall survival to entirely resect the tumor (Simon, et al., 2013, von Allmen, et al., 2017). In contrast, gross total resection of the high risk L2 tumors is associated with an improved prognosis (Adkins, et al., 2004, Matthay, et al., 1998, Mullassery, et al., 2014, Park, et al., 2009). Thus, the benefit must be weighed against the risk of surgery. Surgical resection is often accompanied by a number of complications, some severe and long lasting. Patients can have life threatening hemorrhage during surgery, and later can have bowel injury with nausea, vomiting and severe diarrhea, preventing enteral feeds for a prolonged period of time after surgery. There are often renal complications given the tumor proximity to the kidneys and renal vasculature, infrequently requiring dialysis. These complications can often delay the next cycle of chemotherapy or stem cell transplantation, leaving the patient susceptible to tumor recurrence while healing.

Myeloablative consolidation therapy after surgery has been shown to significantly improve outcome (Berthold, et al., 2005, Matthay, et al., 1999, Pritchard, et al., 2005). For autologous stem cell transplantation, the peripheral blood stem cells are usually collected by apheresis from the patients after two cycles of chemotherapy, as studies have shown satisfactory yield

without significant contamination at that time point (Kreissman, et al., 2013, Park, et al., 2011). Some groups, however, prefer to collect after induction chemotherapy, based on the premise that there would likely be a lower risk of tumor cell contamination, although overall yields of CD34 cells would be lower. Purging these collected stem cells of neuroblastoma cells did not change the event free survival in a randomized trial, and is no longer routinely recommended (Kreissman, et al., 2013). The optimal conditioning regimen for myeloablation is still under study. Total body irradiation was initially used but did not provide apparent benefit over dose intensive chemotherapy regimens and has significantly more long-term effects so it is no longer routinely used (Saarinen-Pihkala, et al., 2012). A single transplant with carboplatin, etoposide and melphalan (CEM) conditioning regimen was studied, with SIOPEN comparing CEM to a single busulfan and melphalan (BuMel) transplant while the COG studied adding a tandem transplant with thiotepa and cyclophosphamide, followed six weeks later by CEM. Both BuMel and tandem transplant were shown to be superior to CEM alone and are now the standard of care in their respective regions (George, et al., 2006, Ladenstein, et al., 2017, Park, et al., 2016, Seif, et al., 2013).

For maintenance therapy, patients are treated with a combination of isotretinoin and anti-GD2 antibody immunotherapy. The former has been shown to promote tumor cell differentiation and slow growth of neuroblastoma cells and has improved event free survival in a randomized trial (Matthay, et al., 1999). Fenretinide, a synthetic retinoid derivative, is under investigation as well (Maurer, et al., 2013). GD2 is a disialoganglioside that is expressed on neuroectodermal tumors including neuroblastoma. The addition of a chimeric monoclonal antibody targeting GD2, known as ch14.18 or dinutuximab, along with GM-CSF and interleukin-2 (IL-2) has been shown to significantly improve event free survival and overall survival over isotretinoin alone, and the combination is now the accepted maintenance therapy (Yu, et al., 2010). The short-term side effects, however, can be significant with common toxicities of fever, allergic reactions, and fluid-overload causing respiratory distress and hypotension. Pain is also a common manifestation, as GD2 is found on peripheral pain fibers, and parenteral opiates are usually required. Further study is ongoing to determine if IL-2, which contributes to this side effect profile, is necessary for the beneficial effect of anti-GD2 antibodies (Siebert, et al., 2016). Anti-GD2 therapy has also been promising earlier in therapy (Talleur, et al., 2017), thus will be included in induction in an upcoming COG trial. In the relapsed/refractory setting, anti-GD2 immunotherapy has recently shown beneficial responses in over half of patients when combined with chemotherapy (Mody, et al., 2017) and when combined with natural killer cell infusions (Federico, et al., 2017). Other methods of targeting GD2 such as a vaccine (Kushner, et al., 2014), humanized antibodies or immunocytokines (Navid, et al., 2014, Shusterman, et al., 2010) and chimeric antigen receptor (CAR) T-cells (Louis, et al., 2011) are under investigation.

Overall 5-year survival from high risk neuroblastoma has improved significantly over the past 20 years, from 29% for patients diagnosed from 1990 to 1994 to 50% for patients diagnosed from 2005 to 2010 (Pinto, et al., 2015). It is thought that the intensification of therapy through myeloablative therapy and immunotherapy have led to this progress. Patients with refractory or relapsed neuroblastoma, however, can rarely be cured. Nevertheless, current salvage therapies can offer partial or even complete response with

improvement in symptoms and quality of life. The most commonly used conventional cytotoxic chemotherapies in this setting are topotecan with either cyclophosphamide or temozolomide (Di Giannatale, et al., 2014) or irinotecan and temozolomide (Bagatell, et al., 2011, Kushner, et al., 2006, London, et al., 2010). Radiation therapy can be used locally to provide symptomatic relief, especially at sites of boney disease.

Another form of salvage therapy is ^{131}I-mIBG therapy. This has the same localizing properties as ^{123}I-mIBG used for imaging, but has higher amounts of the radioactive isotope, which also has a longer half-life, thus delivering a focal dose of radiation to all the tumor sites. A 30–40% response rate has been observed in refractory and relapsed neuroblastoma (Matthay, et al., 2007, Wilson, et al., 2014, Zhou, et al., 2015), and studies using it in upfront therapy are underway. A randomized COG trial will study the inclusion of ^{131}I-mIBG during induction therapy. This therapy can be beneficial but logistically difficult as patients must be kept in isolation for multiple days until they are no longer radioactive, and only certain centers can provide this safely.

Targeted small molecule inhibitors are also being developed in neuroblastoma, some showing activity in the relapsed setting, which can provide an oral life-prolonging option. ALK inhibitors are appropriate in patients whose tumors harbor activating *ALK* mutations (Mosse, et al., 2013). Some of these mutations, such as F1174L, however, are resistant to the current ALK inhibitors (such as crizotinib) and a new inhibitor formulated to overcome this resistance, lorlatinib, (Infarinato, et al., 2016) is actively being evaluated in the New Approaches to Neuroblastoma Therapy (NANT) consortium. Aurora kinase inhibitors are known to cause cell cycle arrest, but they have also been found to destabilize MYCN which is particularly appealing given that there are no direct inhibitors available targeting this driver in neuroblastoma (Gustafson, et al., 2014). Indeed, an aurora kinase inhibitor, alisertib, combined with chemotherapy showed promise in a phase I trial and further studies are ongoing (DuBois, et al., 2016, Mosse, et al., 2012). In an attempt to block the Ras pathway, sorafenib, which is a Raf kinase inhibitor, (Kakodkar, et al., 2012) and newer PI3K inhibitors are being studied in children with neuroblastoma (Chanthery, et al., 2012, Erdreich-Epstein, et al., 2017). VEGF inhibition paired with inhibition of Nutlin-3A showed promising effects *in vivo* (Patterson, et al., 2011), thus bevacizumab is now in clinical trials in neuroblastoma combined with chemotherapy. *TRK* fusions have been discovered in many tumor types, including neuroblastoma (Vaishnavi, et al., 2015), and TRK inhibitors have shown partial responses and stable disease in a Phase I NANT trial (Minturn, et al., 2011) so remains under intense study. Checkpoint inhibitors are an exciting new target in cancer therapy (Cole, et al., 2011, Russell, et al., 2013), and phase I study with a CHK1/2 inhibitor in children with relapsed solid tumors is ongoing. Another interesting target in neuroblastoma is ornithine decarboxylase (ODC) which is the rate-limiting enzyme in polyamine synthesis, as it is a downstream target of MYC. Difluoromethylornitine (DFMO), an ODC inhibitor, is being studied in neuroblastoma in the relapsed setting as well as for maintenance (Evageliou, et al., 2016, Rounbehler, et al., 2009, Saulnier Sholler, et al., 2015). Other inhibitors in various stages of investigation include bromodomain inhibitors (Henssen, et al., 2016, Puissant, et al., 2013), and histone deacetylase inhibitors (DuBois, et al., 2015, Fouladi, et al., 2010). Further immunotherapy is also understudy in neuroblastoma in early phases with PD1 inhibitors (Wagner and Adams, 2017), CAR-T cells (Heczey, et al., 2017),

and NK cells (Talleur, et al., 2017). As the safety and efficacy of these inhibitors are elucidated, the more promising could eventually be incorporated in upfront therapy, ideally improving survival before relapse.

Summary

Detailed, evidence-based risk stratification in neuroblastoma has allowed for intensification of therapy for the highest risk patients while decreasing therapy in the low risk patients. Overall outcomes have been improving as a result, but further work is needed to continue this progress. The treatments discussed here for relapsed and refractory patients are targeted therapies and immunotherapy, which, as further research develops, could potentially be included in initial therapy of newly diagnosed patients, with fewer complications and better efficacy.

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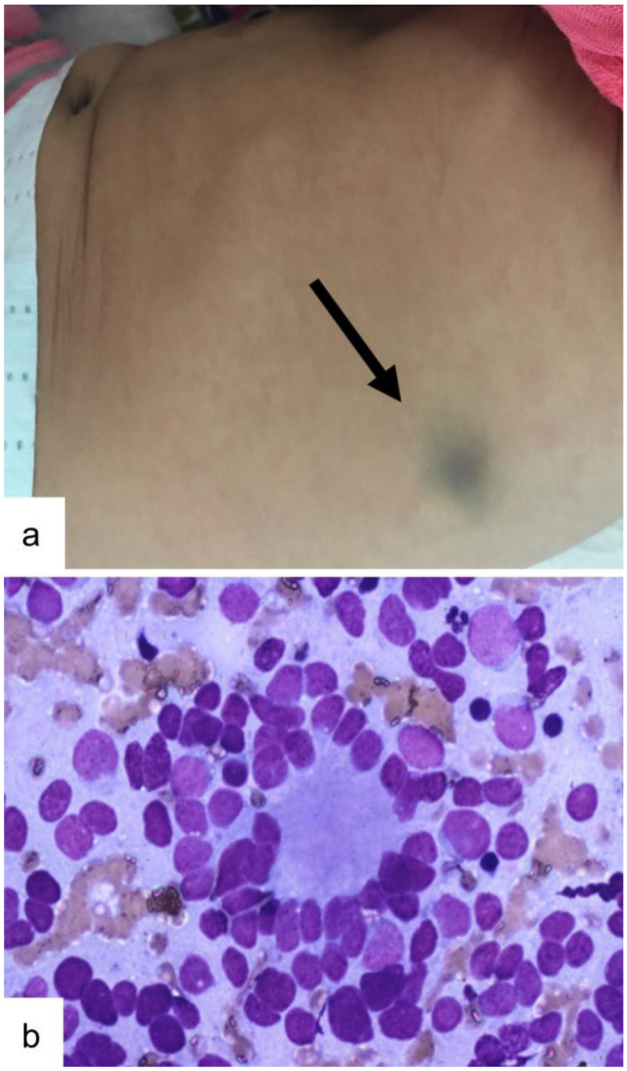

Figure 1. Skin Metastasis in Infant with Stage MS Neuroblastoma

A) Skin metastasis in neuroblastoma can be seen in stage MS disease, consisting of subcutaneous nodules with a bluish hue. B) Fine needle aspirate of a skin metastasis showing histology consistent with neuroblastoma, here showing a Homer-Wright rosette pattern.

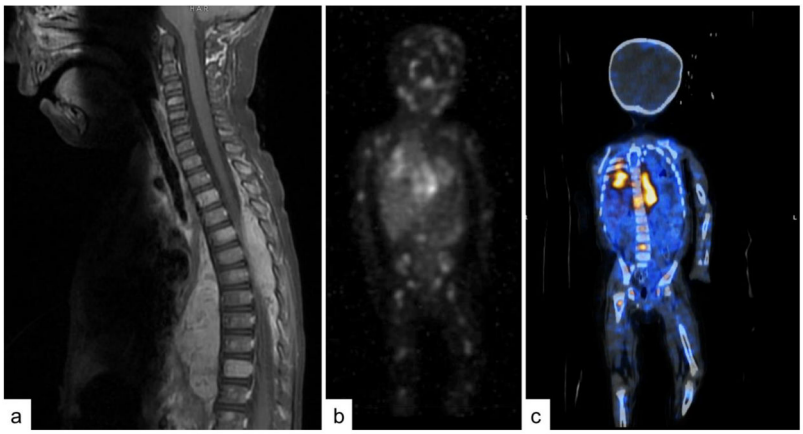

Figure 2. Imaging in Neuroblastoma

Imaging in neuroblastoma must be multimodal to accurately locate and characterize the primary tumor with cross-sectional imaging and locate metastatic disease with MIBG. A) An MRI showing a paraspinal mass invading the spinal canal across many thoracic levels, causing spinal cord compression. Also note the metastatic involvement of multiple vertebral bodies. B) ^{123}I-metaiodobenzylguanidine (MIBG) scan showing the primary thoracic tumor and revealing wide spread metastatic disease involving the bones. C) Single-photon emission computed tomography (SPECT) combining MIBG and CT to better localize the MIBG uptake.

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

Figure 3. International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification Schema

Reprinted with permission. ©2009 American Society of Clinical Oncology. All rights reserved. Cohn, S et al: J Clin Oncol 27(2), 2009: 289–297. This is the original published INRG risk classification. All blank fields represent any value. GN, ganglioneuroma; GNB, ganglioneuroblastoma; Amp, amplified; NA, not amplified.

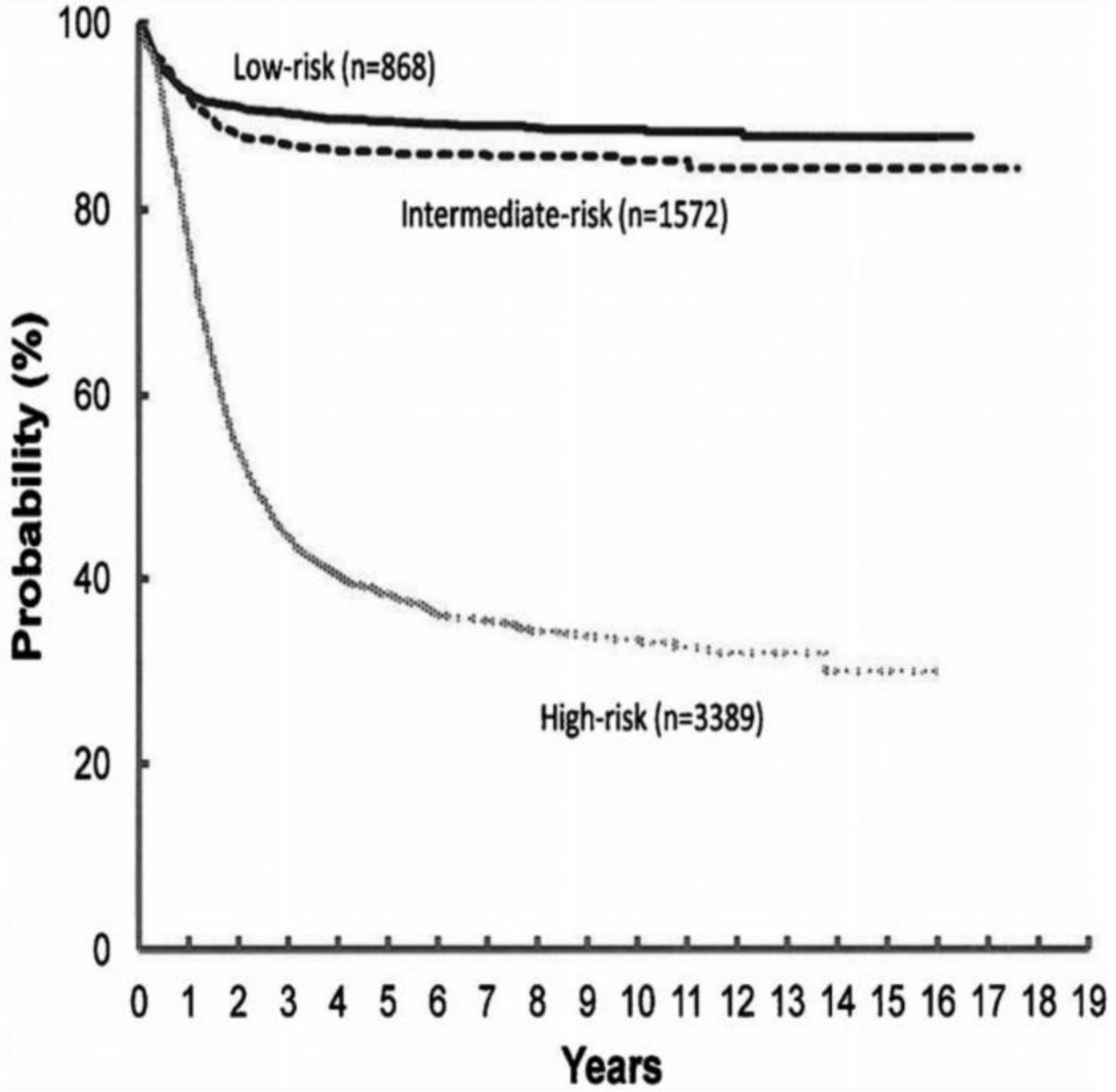

Figure 4. Event Free Survival Based on Risk Stratification (reproduced with permission from (Park, et al., 2013))

Patients with high risk disease have significantly worse event free survival than those with low or intermediate risk disease. Event free Kaplan-Meier survival curves from the time of diagnosis for children enrolled on Children's Oncology Group, Children's Cancer Group or Pediatric Oncology Group studies between 1990 and 2010. Risk stratification based on INRG risk classification.

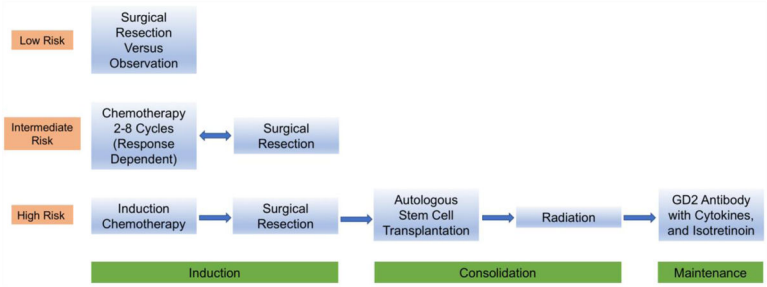

Figure 5. Treatment Overview for Neuroblastoma by Risk Classification

Patients with low risk disease are often managed with surgical resection or observation alone with tumors likely to spontaneously regress that are not causing symptoms. Intermediate patients are treated with chemotherapy with the number of cycles dependent on their response as well as surgical resection of the primary tumor. High risk disease requires intensive multimodal therapy, including chemotherapy, surgery, myeloablation, radiation, immunotherapy and differentiation therapy.

Table 1
International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow