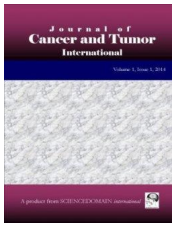

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Neuroblastoma: Current Imaging and Therapeutics

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Authors' contributions

This work was carried out in collaboration between all authors. Author AKP performed literature search and wrote major portion of the manuscript. Author KKP contributed to literature search and manuscript editing. Author EMR wrote the MRI/MRS sections related to neuroblastoma imaging and characterization. Author XH initiated the project, outlined the scope of manuscript, and performed final editing. All authors read and approved the final manuscript.

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ABSTRACT

Neuroblastoma is the most common solid abdominal tumor in children under the age of 2 years and accounts for approximately 15% of childhood mortality due to cancer. Its clinical behavior can vary from spontaneous regression to rapid fatal progression and anywhere in between (e.g. differentiation into benign tumors). Unfortunately, 50% of patients already have metastases at presentation. This marked clinical variability and often advanced presentation at time of diagnosis must be addressed with improved imaging and new treatments, particularly through focus on expanded drug development. Current treatment regimens (surgical resection, chemotherapy, and

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radiotherapy) have proven to be inadequate for treating advanced disease and frequently cause severe side effects that make them intolerable for many children. Promising new therapies include anti-adhesion therapy and immunotherapy, which uses antibodies to trigger a patient's own immune system to destroy neuroblastoma cells. Of particular interest in the realm of anti-adhesion is attenuation of NF-κB over-activation. Increased NF-κB activity is thought to play a role in the development of tumor resistance to chemotherapeutic agents and radiation. Therefore, novel drugs to attenuate NF-kB activity could revolutionize treatment by increasing overall treatment effectiveness and allowing for reduced drug and radiation doses for dose-sensitive patients.

Keywords: Neuroblastoma; immunotherapy; anti-adhesion; NF-κB activity; neuroblastoma imaging; neuroblastoma therapeutics.

1. INTRODUCTION

Neuroblastoma, a tumor that derives from the sympathetic nervous system and most often manifests as an abdominal mass originating from the adrenal glands, is the most common extracranial solid tumor of childhood and accounts for approximately 15% of childhood mortality due to cancer [1]. New treatments for neuroblastoma are needed because current treatment options are self-limited by their side-effects and decreased effectiveness as the disease progresses. As part of disease management, patients receive an extensive workup involving multiple imaging modalities and biochemical testing to categorize them as high-risk, medium-risk, or low-risk. Although strides have been made in optimizing the use of imaging modalities and therapies for neuroblastoma, high-risk patients continue to exhibit a survival rate of only less than 40% [2,3]. Part of the complexity of managing neuroblastoma patients is that the clinical behavior of the tumor is variable, ranging from spontaneous regression, differentiation into benign tumors, and rapidly progressive metastatic disease [1-3]. This review paper details the complexity of this disease, including current guidelines on its management as well as a call to further develop new therapies that address the challenges of advanced disease and its side effects, particularly focusing on immunotherapy and anti-adhesion therapies.

2. CHARACTERISTICS OF NEURO-BLASTOMA PATHOLOGY

Neuroblastoma is an embryonal malignancy of the sympathetic nervous system and the most common extracranial solid tumor in children under the age of 2, with 90% of cases occurring before the age of 5. It accounts for approximately 8 to 10% of pediatric malignancies and 15% of all pediatric cancer-related deaths [1-4]. Solid tumors often begin in the form of a lump or mass in one of the adrenal glands and present clinically as an abdominal mass but can also develop in nerve tissues of the neck, chest, abdomen, or pelvis [5-7].

Neuroblastoma, as discussed in this article, should not be confused with esthesioneuroblastoma (also known as olfactory neuroblastoma) which is believed to arise from the olfactory epithelium and is not a sympathetic nervous system malignancy [8,9].

2.1 Clinical Presentation

The most common clinical symptoms of neuroblastoma include abdominal mass, pain (34%), fever (28%), and weight loss (21%), depending on tumor size and extent of metastatic disease. Lower stage disease most commonly presents as a painless abdominal mass found incidentally via testing for unrelated medical conditions. Rare but highly indicative characteristics of neuroblastoma include lower limb paresis due to intraspinal epidural extension of a primary paraspinal tumor (4%), severe diarrhea refractory to standard treatment due to excessive production of vasoactive intestinal peptide (VIP) by tumor cells (4%), acute cerebellar encephalopathy manifesting as cerebellar ataxia, rapid and random eye movements (opsoclonus), myoclonic jerks due to unknown metabolic disturbances (2%-8%), Horner syndrome especially in patients with lesions in the cervical or upper thoracic sympathetic ganglia (1%-7%), and hypertension, flushing, and periods of excessive sweating due to increased concentrations of catecholamines (0%-2%) [2].

2.2 Adult vs. Pediatric Disease

Adult cases of neuroblastoma are very rare but have poorer outcomes than pediatric cases.

Tumors tend to be more resistant to chemotherapy and recurrences are common. Biologically, adults are less likely to have MYCN amplification, bone marrow involvement, or elevated urine catecholamines. However, their metastatic lesions are often in unusual locations, such as the lung, liver, or CNS [10,11].

2.3 Etiology

The cause of neuroblastoma is largely unknown. Its development is thought to be related to genetic abnormalities causing accidental cell growth that occurs during normal development of the sympathetic nervous system and the adrenal glands. Many factors have been associated with the occurrence of neuroblastoma, including familial inheritance and environmental factors such as assisted pregnancies, paternal exposure to electromagnetic fields, and prenatal exposure to alcohol, pesticides, or phenobarbital. However, no specific study has confirmed the association of these factors with the development of neuroblastoma [12-14]. In addition, no significant variation in incidence has been noted geographically between North America and Europe or between races [14].

2.4 Genetic Factors

Neuroblastoma has several genetic risk factors, occurring either sporadically or from an inherited mutation. These include MYCN amplification, deletions on chromosomes 1p and 11q, and ALK and Phox2b mutations.

MYCN is an oncogene that encodes transcription factors and its amplification is highly correlated with advanced disease and poorer outcomes. Brodeur et al. [15] noted amplification in 0 of 15 patients (0%) with stage 1 or 2 disease but in 24 of 48 patients (50%) with stage 3 or 4 disease. Deletions on chromosomes 1p36 and 11q23 result in loss of heterozygosity (LOH) and poorer prognosis. LOH at 1p36.31 occurs in up to 36% of all primary tumors and is associated with MYCN amplification, decreased overall survival (OS), and decreased event-free survival (EFS). LOH at 11q23.3 is found in greater than one third of primary tumors but rarely associated with MYCN amplification [1]. Normal cells in the human body are diploid, with 2 copies of 23 chromosomes for a total of 46 chromosomes. Most neuroblastoma cells (55%), however, are near-triploid with 58-80 chromosomes, while the rest are near-diploid (35-57 chromosomes) or near-tetraploid (81-103 chromosomes). Interestingly, patients with near-triploid cells tend to have a better prognosis and higher survival rates than those with near-diploid or near-tetraploid tumors [16].

While the vast majority of neuroblastoma cases are sporadic, 1-2% are inherited in an autosomal dominant pattern. Most of these inherited cases are caused by mutations in the anaplastic lymphoma kinase (ALK) oncogene on chromosome 2p23. ALK is a tyrosine kinase expressed in the developing nervous system and these mutations result in constitutive activation and increased kinase activity [1,17]. A smaller portion of inherited neuroblastoma cases are caused by missense or nonsense mutations in PHOX2B, a homeobox gene involved in the development of the autonomic nervous system. These mutations increase neuronal proliferation and dedifferentiation, predisposing cells to tumorgenesis [18].

2.5 Clinical Behavior & Prognostic Factors

Neuroblastoma is one of the rare human malignancies known to demonstrate contrasting patterns of clinical behavior. It has several different evolutive patterns, including spontaneous regression from an undifferentiated state, benign maturation, ganglioneuroma, life-threatening progression, or metastatic disease. Only “age” and “stage” seem to predict the course of disease. For instance, metastatic disease is associated with poor survival in 55% of patients with neuroblastoma who are older than 1 year and 40% of patients with neuroblastoma at all ages even with intensive therapy [2]. Around 10% of tumors undergo spontaneous regression in the absence of or with minimum therapeutic intervention. Interestingly, neuroblastomas exhibit spontaneous regression 10 to 100 times more frequently than any other form of human cancer [13], often associated with a clinically recognizable syndrome called 4S as defined within the International Neuroblastoma Staging System (INSS). In stage 4S, neuroblastoma manifests as a small primary tumor in the abdomen or thoracic cavity accompanied by metastasis to the liver or bone marrow and/or skin but not in the cortical bone. Although spontaneous regression is most commonly observed in stage 4S, it is also well described in children and adults with disease stages 1 to 3 [19,20]. Spontaneous maturation to a benign state, i.e. ganglioneuroma, is much more rare than spontaneous regression.

However, little is known about the incidence and development of ganglioneuromas because they are not often reported in worldwide tumor registries [21].

2.6 Diagnosis and Staging

The diagnosis of neuroblastoma is defined as pathologic confirmation of tumor tissue or evidence of neuroblastoma tumor cells in the bone marrow with increased urine or serum catecholamines (i.e. dopamine) or catecholamine metabolites (i.e. VMA and HMA) [3].

The incidence of patients with low-stage disease has increased due to increased screening. At 6 months of age, a 24-hour urine collection is checked for elevated levels of homovanillic acid (HMA) and vanillyl mandelic acid (VMA). However, this practice has not decreased the diagnosis of high-stage neuroblastoma in patients over the age of 1 year. Whether neuroblastoma rapidly progresses to high-stage disease after the age of 1 year or a significant portion of advanced stage tumors develop from early infancy remains unclear [2].

Current staging criteria are based on the International Neuroblastoma Staging System (INSS) [22] or the International Neuroblastoma Risk Group Staging System (INRGSS). INSS is more surgically based and staging of locoregional disease can vary significantly based on the extent of surgical resection, while INRGSS focuses more on clinical criteria and image-defined risk factors as outlined below [23] (See Table 1).

Table 1. Comparison between INSS and INRGSS [23]

INSS	INGRSS
Stage 1: Localized tumor with complete gross excision; +/- microscopic residual disease; representative ipsilateral lymph node negative for tumor microscopically	Stage L1: Localized tumor not involving vital structures as defined by IDRFs and confined to one body compartment
Stage 2A: Localized tumor with incomplete gross excision; representative ipsilateral lymph node negative for tumor microscopically	Stage L2: Locoregional tumor with presence of one or more IDRFs
Stage 2B: Localized tumor with or without complete gross excision; ipsilateral lymph node positive for tumor microscopically; enlarged contralateral lymph nodes should be negative microscopically	Equals stage L2
Stage 3: Unresectable unilateral tumor infiltrating across the midline; +/- 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	Equals stage L2
Stage 4: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs	Stage M: Distant metastatic disease (except stage MS). Distant lymph node involvement is metastatic disease. Ascites and pleural effusion, even if malignant cells are present, do not constitute metastatic disease unless they are remote from the primary tumor
Stage 4S: Localized primary tumor in infants younger than 1 year (localized as in stage 1, 2A, or 2B) with dissemination limited to skin, liver, or bone marrow (<10% malignant cells)	Stage MS: Metastatic disease in children <547 days (18 months) of age with metastases confined to skin, liver, and/or bone marrow (<10% malignant cells); MIBG scan must be negative in bone and bone marrow. Primary tumor can be L1 or L2 with no limitations in terms of crossing or infiltration of the midline.

IDRFs: image-defined risk factors

To diagnose neuroblastoma according to INRGSS, three dimensional measurements of the primary tumor and assessment of image-defined risk factors are required [23]. INRGSS is designed to be primarily used at the time of diagnosis and requires the use of CT or MRI in addition to 123-iodine (^{123}I) metaiodobenzylguanidine (MIBG) scintigraphy. INRGSS also does not take into account midline and lymph node involvement whereas INSS does. Moving forward, it is likely that both staging systems will be used in parallel in future group cooperative studies [1].

2.7 Risk Categories

The Children's Oncology Group (COG) stratifies disease into low, intermediate, and high risk categories based on age, stage, MYCN amplification, DNA ploidy, and the International Neuroblastoma Pathologic Classification (INPC) system. Probability of prolonged disease-free survival is 95-100% for low-risk disease, 85-90% for intermediate-risk disease, and <30% for high-risk disease [16].

In 2008, the International Neuroblastoma Risk Group (INRG) classification system was developed to standardize pre-treatment risk stratification. Risk categories are based on 5-year event-free survival (EFS), as determined by age, INRG stage, histologic category, grade of differentiation, MYCN status, chromosome 11q status, and DNA ploidy. Patients with expected 5-year EFS >85% are considered very low-risk while those with >75% to 85% expected 5-year EFS are deemed low-risk. Furthermore, those with an expected 5-year EFS of 50 to 75% are considered intermediate-risk while those with <50% expected 5-year EFS are deemed high-risk [25].

3. IMAGING MODALITIES

Imaging plays an important role in the investigation of patients with neuroblastoma, including initial staging, evaluation of treatment efficacy, and surveillance [26,27]. A number of different imaging modalities are used, including computerized tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), MIBG scans, bone scintigraphy, FDG-PET, somatostatin receptor scintigraphy (SRS), and radiolabed antibodies. The pros/cons and specific uses of each are considered below.

3.1 Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI)

Standard imaging modalities for assessing patients with neuroblastoma include CT or MRI. They are part of the initial diagnostic testing to evaluate primary tumor size, regional extent, and distant spread to the neck, thorax, abdomen, or pelvic sites. However, these scans are recommended as part of the workup only in patients with neurologic symptoms or if there is a clinical indication based on physical exam.

Table 2. COG neuroblastoma risk stratification [24]

INSS stage	Age	MYCN status	INPC histology	DNA index	COG risk group
1	0-21 years	Any	Any	Any	Low
2A/2B	<365 days	Any	Any	Any	Low
	365 days-21 years	Non-Amplified	Any	-	Low
	365 days-21 years	Amplified	Favorable	-	Low
	365 days-21 years	Amplified	Unfavorable	-	High
3	<365 days	Non-Amplified	Any	Any	Intermediate
	<365 days	Amplified	Any	Any	High
	365 days-21 years	Non-Amplified	Favorable	-	Intermediate
	365 days-21 years	Non-Amplified	Unfavorable	-	High
	365 days-21 years	Amplified	Any	-	High
4	<365 days	Non-Amplified	Any	Any	Intermediate
	<365 days	Amplified	Any	Any	High
	365 days-21 years	Any	Any	-	High
4S	<365 days	Non-Amplified	Favorable	>1	Low
	<365 days	Non-Amplified	Any	=1	Intermediate
	<365 days	Non-Amplified	Unfavorable	Any	Intermediate
	<365 days	Amplified	Any	Any	High

In the event that brain imaging is indicated, MRI is the radiographic study of choice due to its superior capabilities in elucidating spinal cord involvement and extension into the epidural space [28-33]. With gadolinium enhancement, the primary tumor often appears heterogeneous. Compared to CT, MRI is superior in assessing for leptomeningeal or epidural extension, extent of cortical bone destruction, and tumor invasion of the kidneys, liver, bone marrow, and diaphragm [26].

One prospective multi-institutional study that compared the accuracy of CT or MRI alone in conjunction with bone scintigraphy for staging neuroblastoma patients showed that MRI was a much more sensitive test (83%) compared to CT (43%) [34]. Other advantages of MRI include lack of ionizing radiation and superb definition of primary tumor with high intrinsic soft-tissue contrast resolution which allows for determination of internal structures. For these reasons, MRI has begun to replace CT scans in many centers. Although calcification is not readily identified on MRI and small lymph nodes less than 13 mm are difficult to ascertain, necrosis, cystic areas, and hemorrhages are readily seen. Bone marrow and cortical involvement can be successfully assessed via MRI but false positives for bone marrow involvement have been noted after treatment in some cases [35]. Therefore, bilateral posterior iliac crest marrow aspirates and core biopsies must be performed to exclude bone marrow involvement [22,36].

CT is useful in defining the site/extent of tumor and in assessing for evidence of regional invasion, vascular encasement, and lymphadenopathy. It is also used to easily detect characteristic radiographic findings such as soft tissue calcifications which are highly suggestive of neuroblastoma and occur in 80-90% of patients [26,34,37,38]. Furthermore, CT is integral in differentiating neuroblastoma from Wilms' tumor as these are the two leading causes of an abdominal mass presenting in childhood [39,40].

3.2 Magnetic Resonance Spectroscopy

While structural MRI is a crucial tool in the assessment of neuroblastomas, it typically provides very little physiological information. The ability of magnetic resonance spectroscopy (MRS) to probe tissue biochemistry is a powerful tool that adds to the information obtained by conventional MRI.

Proton magnetic resonance spectroscopy (1H MRS) offers the unique ability to measure metabolite levels in a non-invasive manner. In the normal brain, the most prominent peak arises from N-acetylaspartate (NAA) at 2.02 ppm. NAA serves as a marker of neuronal density and viability and is typically decreased or completely absent as neurons are replaced by neoplastic tissue. The other major peaks include total creatine [creatine (Cr) + phosphocreatine (PCr)] which is a marker for brain energy as well as choline containing compounds (Cho) which are observed at 3.03 and 3.2 ppm respectively. Pathological alterations in membrane turnover or inflammatory and gliotic processes result in a massive increase in MRS-visible Cho [41]. Thus, elevated choline is the hallmark of brain cancers as well as cancers in other tissue. Furthermore, it has been established that an increase in Cho is directly related to tumor malignancy [42].

Under normal conditions, one should not be able to observe lactate (Lac) as the Lac concentration is very low in the adult brain. Accelerated anaerobic glycolysis occurs in highly cellular metabolic lesions which have begun to outgrow their blood supply. Consequently, the presence of Lac may indicate high level of malignancy [43,44].

Other metabolites detected by 1H MRS include myo-Inositol, glycine (Gly), taurine, and glutamine/glutamate. High concentrations of Gly are observed in high-grade gliomas compared to low-grade gliomas [45,46]. Pediatric patients with untreated primitive neuroectodermal tumors (PNETs) have demonstrated elevated taurine concentrations, making MRS useful in the differentiation of PNETs from other tumors including astrocytoma, pilocytic astrocytoma, and ependymoma [47].

Lindskog et al. [48] showed that response or resistance to chemotherapy was accurately predicted by 1H MRS. A treatment response to chemotherapy was characterized by a significant increase in mobile lipid/choline and mobile lipid/methyl ratios, increased levels of polyunsaturated fatty acids, and a significantly decreased Cho resonance in a dose and time dependent matter. This metabolic response precedes effects on tumor volume and may accurately predict tumor regression [49].

Lastly, 31P MRS, used to visualize phosphorus, can measure phosphodiester compounds (PDE) and phosphomonoester compounds (PME). In

tumors, PDE and PME are typically elevated due to rapid membrane synthesis [50].

3.3 MIBG Scans

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog and is taken up by cells through the norepinephrine transporter (NET). When attached to radioactive iodine, this MIBG uptake can be visualized and used for disease staging and monitoring. The normal physiological biodistribution of MIBG includes the liver, myocardium, salivary glands, intestines, kidneys, and thyroid. Mild uptake is seen in the adrenal glands [51-54]. MIBG uptake will be seen in 90% to 95% of patients with neuroblastoma at the site of the primary tumor and sites of metastases such as bone, bone marrow, and lymph nodes. While metastases to the central nervous system are uncommon, MIBG is not as accurate in their evaluation as ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) when they are present. This is because tumors that are MIBG negative have very poorly differentiated cellularity (i.e. exhibit de-differentiation) and are unable to metabolize the MIBG [55].

When MIBG is used, ^{123}I MIBG is generally preferred to ^{131}I MIBG because it is more sensitive and thereby results in higher image quality. This translates to a need for fewer scans with less risk of damage to the thyroid gland [56-62]. The size of the tumor may reflect whether the uptake is uniform or irregular with focal areas of reduced uptake indicating central necrosis versus de-differentiation which is characteristic of more malignant clones of neuroblastoma. Although not confirmed, it is a commonly held belief that well differentiated tumors show lower MIBG uptake in vivo. Because the uptake of MIBG is directly dependent on catecholamine transporters, patients on medications such as TCAs, phenylpropanolamine, pseudoephedrine, and labetolol will show reduced uptake because the mechanism of action of these drugs is to block catecholamine uptake [63-67]. If the MIBG scan is negative, a FDG-PET scan should be done in addition to a technetium bone scan to evaluate a patient for cortical bone disease [68-70].

In addition to use in staging, MIBG scans can also serve as a prognostic indicator and even as therapy. In terms of prognosis, a scoring system for MIBG scans has been described by Suc and colleagues in which patients with MIBG scores lower than 4 have a higher probability of achieving complete response after induction therapy [71]. Furthermore, Katzenstein and colleagues reported that MIBG scores >3 correlate to ultra high-risk patients who are more likely to relapse after therapy. A strong correlation exists between event-free survival and post-induction MIBG score [71-76].

In terms of therapy, ^{131}MIBG has been used in the form of radiotherapy but its use has remained controversial because of a large variation in response rates (ranging from 20% to 60%) in newly diagnosed and relapsed or refractory patients in addition to significant side effects such as bone marrow depression requiring autologous bone marrow transplant (ABMT) with high doses [77]. Its effectiveness in the palliative setting for pain control is well documented [78]. In a review of MIBG therapy by Tepmongkol and Heyman in 1999, cumulative results from the literature for MIBG therapy in 276 neuroblastoma patients revealed complete remission in 17 patients, partial remission in 70 patients, stable disease in 88 patients, and progressive disease in 74 patients. 27 patients were unevaluable and the objective response rate was 34.9% [78]. The European Association of Nuclear Medicine determined an objective response rate of 51% based on pooled results from 229 patient in 1999 [79].

3.4 Bone Scintigraphy

Bone scintigraphy is another form of imaging used for staging purposes. Total body radionuclide bone scintigraphy uses 99mTc-disphosphonate compounds to detect cortical skeletal metastases in a process that is more sensitive than conventional skeletal radiography. The metastatic pattern seen in bone in neuroblastoma patients is typically a symmetrical pattern in the metaphyseal portion of long bones. Often, it is difficult to ascertain metastases in metaphyseal regions of long bones due to frequently normal epiphyseal uptake on bone scintigraphy. On the blood pool phase of bone scintigraphy, the normal growth plate has a well-defined linear appearance with clear demarcation between plate and metaphysis whereas symmetrical flaring and blurring of the growth plate with extension into the metaphysis is suggestive of metastasis. Focal abnormalities commonly found in patients with neuroblastoma include the orbits, the parasagittal areas of the skull, and multiple “hot” and “cold” lesions in the spine [80]. Bone scintigraphy can also be used to differentiate cortical metastases from bone

marrow metastases, an important distinction since cortical metastases carry a much worse prognosis. The usefulness of bone scintigraphy is more controversial in terms of restaging to assess treatment response; conflicting evidence exists as to whether it adds any valuable information to findings on MIBG studies when assessing response to treatment [81-85].

3.5 FDG-PET

While data on FDG-PET scanning as it relates to neuroblastoma is limited, Kushner et al. found that FDG-PET scanning correlates well with disease status and findings on MIBG scans, though the detection rate of abnormal areas is increased [66]. Even though today's consensus is still that MIBG is superior to FDG-PET, certain organs such as the liver, bone, and bone marrow are better visualized on FDG-PET as opposed to MIBG [86,87]. FDG reflects the increased glycolytic rate of tumor cells. Uptake is therefore proportional to tumor cell burden and tumor cell proliferation [88]. In a study conducted by Shulkin, 16 out of 17 neuroblastoma patients exhibited FDG uptake by primary tumors and metastases which led to the conclusion that the majority of neuroblastomas were metabolically active and PET detectable [89]. However FDG-PET is not useful for identifying metastases to the brain because the brain has increased (high normal) FDG uptake at baseline. FDG-PET has high utility in patients with a negative MIBG scan and in patients with lesions in the neck region where the resolution and co-registration of the FDG study with CT allows for better evaluation of the lesion and response to treatment [89]. 11-C-hydroxyephedrine (HED) is another agent that is useful with PET because it reaches a sensitivity of 99% for detecting lesions even with a shorter half-life. Overall, while false positives have been noted with PET scanning, it is useful to identify physiological variants [87,90].

Table 3. Comparison of imaging modalities

Imaging	Advantages	Disadvantages
CT	• Quick, commonly available • Can detect calcifications • Can differentiate between neuroblastoma & Wilms tumor	• Less sensitive than MRI • Exposure to ionizing radiation
MRI	• Greater sensitivity than CT • Lack of ionizing radiation • Able to detect leptomeningeal or epidural extension, extent of cortical bone destruction, and invasion of the kidneys, liver, bone marrow, or diaphragm	• Longer duration than CT
MRS	• Measures tissue physiology	• Not commonly available
MIBG Scan	• Can be used for imaging and therapeutics	• Less accurate than FDG-PET when evaluating CNS metastases • Risk damage to thyroid gland • May be influenced by medications
Bone Scintigraphy	• More sensitive than conventional skeletal radiography	• Limited to bony metastases • May be difficult to detect metaphyseal bone metastases
FDG-PET	• Superior to MIBG to evaluate certain organs such as liver, bone, and bone marrow	• Overall inferior to MIBG scan
Somatostatin Receptor Scintigraphy	• May provide information about genetic favorability of tumor	• Variable results, even within same tumor • Less sensitivity than MIBG • Not commonly used
Radiolabeled Antibodies	• Greater sensitivity than MRI or MIBG	• Not commonly available

3.6 Somatostatin Receptor Scintigraphy

Another useful imaging modality is somatostatin receptor scintigraphyv (SRS) given that neuroblastoma cell lines and tumors express somatostatin receptors. A number of studies employing scintigraphy with ^{111}In—pentreotide, a radioactive form of the somatostatin analog octreotide, showed that the sensitivity of such imaging is only 55% to 70% when compared to 83% to 94% for MIBG [91-93]. This difference in sensitivities most likely has to do with the fact that only planar imaging is used in octreotide studies. A few studies using SPECT have shown mildly improved sensitivities [26]. Patients with positive octreotide studies tend to have better outcomes because they also tend to have more favorable biological factors such as nonamplified MYCN and hyperdiploid/intact chromosomal 1p36 [26,51,92,93]. In addition, somatostatin receptors are often downregulated in more aggressive tumors and may even vary within a tumor. Therefore, given variability in these receptors among tumors, SRS is not routinely performed because it does not provide any more valuable information over MIBG that would alter patient management [91-93].

3.7 Radiolabeled Antibodies

Radiolabeled antibodies, namely IgG1 monoclonal antibody and anti GD2 antibodies have shown higher sensitivities than even MRI and MIBG but are not readily available. These antibodies are able to bind to specific cell proteins that are expressed on both mature and immature tumor cells and are thereby useful in detecting neuroblastoma lesions. They are especially useful in detecting local tumor recurrences and skeletal metastases earlier than MIBG. Given their complexity, however, these antibodies cannot be routinely employed even though they provide valuable additional information [94,95].

4. MANAGEMENT & THERAPIES FOR NEUROBLASTOMA PATIENTS

4.1 Treatment Options Overview

Treatment options for neuroblastoma include surgical resection, chemotherapy, radiotherapy, and immunotherapy. Choosing appropriate therapy is based on several criteria such as age, stage of disease, and biological/biochemical markers [4]. Patients with localized neuroblastoma tend to have good outcomes. Even with metastatic disease, patients who present before the age of 12 months tend to have much better outcomes than those presenting after the age of 12 months. Presentation with metastatic disease after the age of 12 months is often fatal [96-98] despite treatment. After dissemination to the bone, the survival rate is less than 7% [99]. Therefore, there is an undeniable need to develop new and improved therapies. This is particularly true for patients with metastases, a group that constitutes 50% of patients at presentation [27,37,99,100].

Before any management decisions are made, patients diagnosed with neuroblastoma need to be characterized with having low-risk disease, intermediate-risk disease, or high-risk disease. Therapies are then tailored to patients based on this classification system; surgical resection, chemotherapy, and/or radiotherapy are the available options. Typically, chemotherapy is limited to patients with regional or advanced stage disease while radiotherapy is reserved for those who have advanced disease and unfavorable biologic characteristics [3].

4.2 Low-risk Disease

For low-risk disease, primary treatment is surgery alone. Stage I disease has a 4-year survival rate of >95% with post-surgical relapse effectively treated with salvage chemotherapy. For stage 2A and 2B disease (biologically favorable but not completely resectable), chemotherapy is generally not needed but if used can be given in reduced doses [24]. Infants with 4S disease without MYCN amplification receive supportive care since these tumors often undergo spontaneous regression. Regardless of risk category, if the patient is experiencing life-threatening symptoms (i.e. hepatomegaly causing obstruction, liver dysfunction, or respiratory insufficiency), chemotherapy can be used as initial treatment. Available chemotherapeutic agents include cyclophosphamide, carboplatin, cisplatin, etoposide, and doxorubicin [101-107].

4.3 Intermediate-risk Disease

In intermediate-risk neuroblastoma, the main therapies consist of surgical resection and moderate-dose, multi-agent chemotherapy. For stage 3 and stage 4 disease, histologic and biological factors have great influence on

prognosis. For patients with favorable tumor characteristics, the survival rate is 95% with moderate-dose chemotherapy followed by resection. The recent COG protocol ANBL0531 sought to refine the minimum amount of chemotherapy required to sustain excellent survival rates in intermediate-risk disease. The drug regimen included a combination of cyclophosphamide, carboplatin, etoposide, and doxorubicin. Subjects were given chemotherapy every 21 days for 2, 4, or 8 cycles, followed by surgical resection of the tumor. The number of cycles was based on further risk stratification into 4 treatment groups (based on age, stage, MYCN amplification, DNA ploidy, and histopathology) and was reduced from the previous COG protocol A3961 which used only 4 or 8 cycles [108]. In an effort to address short- and long-term toxicity from chemotherapy, cumulative exposure has been minimized and carboplatin has been substituted for cisplatin due to its improved side effect profile. This reduction reflects the goal of eliminating or at least greatly reducing the use of chemotherapy in these patients. Many studies are also evaluating if other molecular/genetic variables can be used to identify those patients who require chemotherapy [16,109-112].

4.4 High-risk Disease

The management of high-risk neuroblastoma includes induction chemotherapy, local control through resection and radiation, myeloablative consolidation, and treatment of minimal disease with biologic agents. Guidelines for this treatment have largely been established by the Pediatric Oncology Group and the Children's Cancer Group as they have conducted extensive research in this area. Despite multiple treatment options and neuroblastoma's chemo-responsiveness, only 30-40% of patients survive long term [3].

4.5 Induction Chemotherapy

To successfully cure high-risk neuroblastoma, resection of the primary tumor and bulky metastases is necessary. Before surgery, induction chemotherapy is often used to reduce tumor size. Delayed surgical resection, generally after three rounds of induction chemotherapy, may improve resection outcomes, minimize surgical complications, and increase overall survival [113]. A direct correlation exists between achieving complete tumor response after induction therapy and survival [114], while increasing chemotherapy doses may improve initial tumor response rate [115]. In some cases, however, surgery may be more appropriate at diagnosis rather than after induction chemotherapy.

The most common induction regimen involves cycles of cisplatin and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide. The Children's Oncology Group (COG) recently added topotecan, a topoisomerase I inhibitor, after studies showed effectiveness in recurrent neuroblastoma [116].

4.6 Radiation Therapy

With neuroblastoma being one of the most radiosensitive tumors of childhood [5], radiation can be used to enhance the effect of chemotherapy at metastatic sites in some patients [117,118]. In high-risk disease, radiotherapy is also used after surgical resection to achieve maximal local control. Shown to reduce local recurrence after surgery regardless of response to induction chemotherapy, application of external beam radiotherapy (2160 cGy in daily 180 cGy fractions) can be applied to the primary tumor site. The current COG protocol ANBL0532 for high-risk neuroblastoma is evaluating whether increased radiotherapy dosing improves local control. Subjects with complete response to induction chemotherapy receive the usual 2160 cGy, while those with residual disease receive an additional 1440 cGy [119].

Radiotherapy can also be applied to other sites at risk for relapse. If disease advances despite all treatment efforts so far discussed, radiation therapy may also be used for palliative purposes to treat cancer symptoms such as pain and discomfort related to tumor burden. In one retrospective study that evaluated the use of palliative radiotherapy at the Institut Curie in Paris, France, a response rate of 82.4% was noted with response being defined as more than 25% reduction in tumor mass or any reduction in pain. Furthermore, increasing the radiation dosage to greater than 15 Gy increased the response rate to 100%, suggesting a dose-response relationship. However, actual survival for these patients remained dismal, ranging only from 27 to 43 days [120].

4.7 Myeloablative Consolidation Therapy

A promising treatment for high-risk neuroblastoma is myeloablative consolidation

therapy. The CCG-3891 study demonstrated that myeloablative therapy with purged bone marrow transplantation improved outcomes in this patient population [114], while European trials also showed improved outcomes after myeloablative therapy compared with maintenance chemotherapy [121] or observation alone [122]. Continuing this research, the current COG protocol ANBL0532 is trying to determine if intensifying myeloablative therapy results in higher cure rates [16].

Maintenance therapy with isotretinoin after myeloablative therapy is now standard of care during the first remission after studies showed it reduces relapse rates by inducing differentiation and arresting growth of neuroblastoma cells. In a study conducted by Matthay et al. 130 high-risk patients received six cycles of 13-cis-retinoic acid at 160 mg/m^2/day for 14 consecutive days in 28-day cycles after completing chemotherapy followed by myeloablative therapy with no disease progression while 128 similar patients in the control arm received no further therapy. The event-free survival was significantly better for those who received 13-cis-retinoic acid (46+/-6 percent vs. 29+/-5 percent, P=0.027). However, more research needs to be done regarding optimum dosing, response variations, and potential side effects [116,123].

4.8 Immunotherapy

Immunotherapy is an emerging therapy that is promising considering the significant limitations of other therapies in terms of side effect profile and effectiveness in advanced disease. While still in the experimental stage, immunotherapy is used to treat minimal residual disease after patients have undergone chemotherapy and surgical resection. In this type of therapy, monoclonal antibodies directed against neuroblastoma-specific antigens (i.e. gangliosidase, GD2) kill residual neuroblastoma cells via antibody-dependent cellular cytotoxicity. In this way, immunotherapy is essentially designed to train the body's own immune system to detect and destroy neuroblastoma cells that have survived chemotherapy and/or radiation therapy by marking them with these antibodies which have shown excellent targeting in neuroblastoma. 3F8 is one particular IgG3 murine monoclonal antibody directed against the ganglioside GD2 that has shown promise in a number of studies. Logistically, the treatment involves the injection of monoclonal antibody 3F8 into the bloodstream along with GM-CSF (granulocyte-macrophage colony stimulating factor) which stimulates granulocyte/monocyte production to make use of the antibodies via a cytotoxic killing mechanism. GM-CSF also plays a major role in mediating the common side effect of severe myelosuppression [124].

A number of preclinical and clinical trials have also suggested that lymphocyte-, neutrophil- or natural killer cell-mediated antibody-dependent cellular cytotoxicity can be enhanced by co-administration of GM-CSF and interleukin-2 [125,126]. GM-CSF is a monomeric glycoprotein secreted by macrophages, T cells, mast cells, NK cells, endothelial cells, and fibroblasts that functions as a cytokine and stimulates production of granulocytes/monocytes while interleukin-2 is a cytokine involved in determining immunity.

Advancing immunotherapy continues to be investigated in a number of studies and shows considerable promise. In one phase II study conducted through Memorial Sloan-Kettering Cancer Center, 3F8 was administered to 16 patients who had stage 4 neuroblastoma with response seen in 2/7 patients with bony lesions and 3/8 patients with bone marrow lesions. Three patients were reported to be long-term survivors (70-130+ months) after treatment without any further systemic therapy and no delayed neurological problems. This suggests that 3F8 has significant treatment potential [127]. Another study determined that long-term remission can be achieved without autologous bone marrow transplant (aBMT) with 3F8 treatment in patients with minimal residual disease stage 4 neuroblastoma diagnosed at more than 1 year of age. In this study, 14 out of 29 patients survived and 13 out of the 14 remained progression free. Furthermore, the side effect profile of 3F8 was noted to be tolerable in this study. Of note, it was also determined that if human anti-mouse antibody (HAMA) forms as a result of 3F8 treatment, the lysis of neuroblastoma is neutralized [128]. A 2007 study showed that high-dose cyclophosphamide blocks the humoral response to the murine antibody, indicating that high-dose cyclophosphamide has the potential to prevent host rejection of foreign or not fully humanized proteins. Therefore, high-dose cyclophosphamide may be key in improving the efficacy of 3F8 treatments [129]. Another study investigated the use of radioimmunotherapy in neuroblastoma patients using ^{131}I-3F8. Overall survival at 18 months post-treatment was found to be 40% and the antibody was seen in 42

patients to be localized in the primary tumor and metastatic sites which included lymph nodes, bone marrow, and bone [130].

4.9 Anti-adhesion

Cell adhesion molecules (CAM) are glycoproteins embedded within the cell membrane that form a network between each other, the intracellular cytoskeleton, and the extracellular matrix. Through these connections, they mediate cell proliferation, differentiation, and mobility. In human cancer, however, all five CAM classes are dysregulated: integrins, cadherins, immunoglobulin-like CAMs, selectins, and CD44s. Considering their significant role in tumor progression and the side effects of chemotherapy and radiation, CAMs have become a promising target for anti-cancer therapies [131].

Integrins are transmembrane glycoproteins consisting of an α and β subunit. Isomer β_1 is associated with increased extracellular attachment and $\alpha_5\beta_3$ is associated with increased tumor cell migration. MYCN overamplification, an independent risk factor for poor outcomes, is also associated with decreased expression of α_1, α_3, and β_1 [132,133]. Targeted therapy is unlikely, however, because integrins are commonly expressed on normal cells and different isomers often have redundant functions, requiring broad inhibition [131].

Cadherins mediate cell migration during embryogenesis and consist of three different types: epithelial (E), neural (N), and platelet (P). Shimono et al. [134] described the association between increased expression of N-cadherin and decreased motility of neural crest cells. However, N-cadherin is expressed in almost all epithelial cells and would not be a practical therapeutic target.

Selectins mediate leukocyte adhesion to endothelial cells and similarly to cadherins consist of three different types: endothelial (E), lymphocytic (L), and platelet (P). P-selectin has been shown to affect platelet adhesion to neuroblastoma cells, but the role of selectins in neuroblastoma metastasis has not been determined yet [131,135,136].

CD44 has several isoforms and is expressed in many different tissues. Several studies have reported a positive correlation between CD44 expression and favorable disease characteristics. This includes stage, histology, age, younger age, and normal MYCN expression. Furthermore, CD44 has been shown to connect to the actin cytoskeleton, the main regulator of cell motility. Specific CD44 isoforms may have potential as therapeutic targets and need to be investigated further [131,137-139].

There are three Ig-like CAMs currently known to be expressed in neuroblastoma: deleted in colon cancer (DCC), neural cell adhesion molecule (NCAM), and intercellular adhesion molecule-2 (ICAM2). DCC is thought to be a tumor suppressor in colon adenocarcinoma and several studies have suggested that it may play a role in neuroblastoma progression [140]. Combined data from two studies showed an inverse correlation between DCC expression and high-risk disease, while a mutant version of DCC is found in the NB-16 neuroblastoma cell line. However, while DCC is suspected to interact with intracellular actin as the other CAMs do, this has not yet been proven in the literature [131,141].

NCAMs are expressed on the cell surface of neurons and glia. They have multiple isoforms. A 120kDa isoform is expressed in almost all neuroblastoma cases and may affect cell dissociation from the primary tumor during metastasis [142,143]. Another isoform, PSA-NCAM, is normally expressed during embryogenesis and is seen in poorly differentiated neuroblastoma [144]. Interestingly, a 180 kDa isoform is associated with a more favorable histology (i.e. more differentiation) [145].

ICAM2 is normally expressed in low levels by some leukocytes and endothelial cells. It is also seen in neuroblastoma cell lines and primary neuroblastoma tumors. It is associated with a favorable histology in primary neuroblastoma tumors. It has also been associated with decreased cell motility in vitro and the inability to produced disseminated disease in mice. One study showed that 100% of mice injected with low-ICAM2 neuroblastoma cells developed tumors, while 0% of mice injected with high-ICAM2 cells developed tumors [131,146]. This striking difference suggests that ICAM2 may be an important therapeutic target and needs to be investigated further.

Recently, a number of cell adhesion-mediated survival pathways have been identified with key mediators being LFA-1, VLA-4, FAK, ILK, Src, PI3K, Akt, Ras, MEK, Erk, HMG-CoA reductase,

Rho, Rho Kinase, PKC, and NF-κB. Thus, a drug could intervene by attenuating the over-activation of these key mediators that up-regulate the formation of cell adhesion molecules. Such therapies may reduce the required drug and radiation doses for dose-sensitive pediatric patients, thereby decreasing the amount and severity of side effects. Anti-adhesion strategies include targeting surface antigens and inhibiting cell adhesion-associated pathways through drug delivery to inhibit CAM-DR. Today, the preclinical and clinical knowledge about the role of cell adhesion molecules greatly exceeds the number of related drugs developed [147].

Today's anti-adhesion efforts are focusing on NF-kB, a particular transcription factor that enhances the production of inflammatory mediators and serves as a key mediator in a number of signaling pathways involving cell adhesion. Chemotherapy and radiotherapy both appear to induce NF-κB over-expression in tumors and through this mechanism reduce tumor drug and radiation sensitivity [148]. Thus, there is also some suggestion that these aggressive conventional therapies can be avoided in certain cases based on inherent genetic and molecular properties of the tumor as they may not provide significant benefit [149]. From a molecular point of view, NF-κB is a heterodimer containing a p50 and a p65 subunit that is kept from translocating to the nucleus by binding to its inhibitor IkBa. Any of a number of diverse stimuli can activate the pathway to result in phosphorylation of IkBa, ubiquitination of IkBa, and then degradation of IkBα in the 26S chromosome, leading to NF-κB translocation to the nucleus. In the nucleus, NF-κB activates the transcription of many genes involved in tumorigenesis, apoptosis, and inflammation [150-152].

The elucidation of this theory has led to immense amounts of research. In one such study, curcumin, an agent documented to have anti-tumor effects (i.e. suppression of cellular transformation, proliferation, invasion, angiogenesis, and metastasis) against many types of cancer was tested on human neuroblastoma cells and was found to induce apoptosis of 3 neuroblastoma lines (Lan-5, SK-N-SH and Kelly) through an increased induction of apoptosis by inhibition of NF-κB [99]. Furthermore, Hewson and colleagues conducted a study that suggested that fenretinide-induced reactive oxygen species may be responsible for the induction of apoptosis in SH-SY5Y cells via inhibition of the NF-κB pathway. These findings elucidate information that will help focus future development of drugs for neuroblastoma therapy [8].

5. CONCLUSION

Neuroblastoma is a leading cause of cancer-related mortality in very young children due to difficulty in treating it effectively with current standard treatment modalities. Initial presentation is often at an advanced stage and marked variability in tumor characteristics make neuroblastoma particularly difficult to treat. There is a dire need to develop new therapies to treat neuroblastoma, particularly through utilization of promising immunotherapy and anti-adhesion principles. Data suggest that cell adhesion molecules such as CD44 and ICAM2 can be used to decrease cell proliferation and mobility, while attenuation of NF-κB activity may decrease development of tumor resistance to chemotherapy and radiation. For this reason, it is imperative that anti-adhesion drugs be a strong focus in drug development for neuroblastoma.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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