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Pharmacological Management of High-risk Neuroblastoma in Children

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Abstract

BACKGROUND—Neuroblastoma is the most common extracranial solid tumor of childhood. It accounts for 15% of pediatric cancer deaths. Children with high-risk disease have a 3-year event-free survival rate of only 20%. Chemotherapy is the mainstay of the treatment of children with advanced neuroblastoma.

OBJECTIVE—To review and critically evaluate the pharmacotherapy of neuroblastoma.

DATA SOURCES—Peer-reviewed and review literature, 2000–2011.

STUDY SELECTION—All peer-reviewed, published human subjects studies of therapy for neuroblastoma in children were included. Animal model and in vitro studies were included only if they added to the understanding of the mechanism of a proposed or existing human neuroblastoma therapy.

DATA SYNTHESIS—Current therapeutic options for neuroblastoma involve insufficient differentiation of normal from neoplastic tissue. Critically needed new approaches will increasingly exploit targeting of therapy for unique characteristics of the neuroblastoma cell.

CONCLUSIONS—Pharmacotherapy for neuroblastoma still suffers from an inadequate therapeutic window. Enhancement of toxicity for tumor and safety for normal tissues will entail innovation in targeting neuroblastoma cells and rescuing or protecting normal tissue elements.

Introduction

Neuroblastoma (NB) is a nervous system neoplasm that originates in the sympathetic ganglia. It is one of the most common solid tumors in children under the age of 5. NBs are neuroectodermal tumors of embryonic neural crest-derived cells of both neuronal and chromaffin (neuroendocrine) origin.[1] NB accounts for 7% of childhood malignancies and 15% of all pediatric cancer deaths. It has an incidence of 1 in 10,000 children every year[2] and almost 40% of children diagnosed with neuroblastoma are designated as high-risk due to factors such as age above 1 year, presence of disseminated disease at diagnosis, tumor histologic features associated with adverse outcome and tumor cell amplification of the MYCN gene.[3] Childhood NB can present with primary tumor in the abdomen, adrenal

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medulla (65%), neck, paraspinal ganglia (5%), chest (20%) or pelvis (5%).[4] Associated paraneoplastic syndromes include opsomyoclonus or watery diarrhea-hypokalemia syndrome[2]. Anatomic staging of NB is only one component of risk stratification (Table I); other factors contribute to risk and therefore to therapeutic decision-making (Table II). These factors are well-described elsewhere[5–7] and are beyond the scope of this review.

Advanced stage primary tumors are initially biopsied to obtain tissue samples for biomarker and cytogenetic analysis, followed by multi-agent therapy to enable tumor debulking and resection.[6] High-risk patients are typically treated with multimodal therapy, including intensive induction chemotherapy, autologous stem cell harvesting to enable bone marrow rescue following myeloablative consolidation chemotherapy and subsequent surgical resection and radiation at the primary site to optimize local control.[8] Minimal residual disease and relapse are targeted using novel agents including retinoids; nevertheless disease progression causes a high mortality in this group of patients.[9]

Chemo- and/or radiation therapy can also be used initially to reduce the size of an unresectable tumor at the primary site and the sites of metastasis prior to definitive surgery. Administration of neoadjuvant chemotherapy with anthracycline antibiotics (doxorubicin), epipodophyllotoxins (etoposide), camptothecins (topotecan/irinotecan), alkylating agents (cyclophosphamide/ifosfamide), vinca alkyloids (vincristine), and heavy metals (cisplatin/carboplatin).[6,10] helps to reduce the loco-regional tumor and prevents chemotherapeutic resistance.[2] Radiation is typically administered in combination with chemotherapy following surgical resection. External beam radiation therapy in conjunction with chemotherapy for NB has decreased local recurrence for high-risk disease postoperatively and improved resectability for advanced-stage disease.[2]

One of the challenges following chemotherapy and surgery is the presence of minimal residual disease. Immunotherapy has been proposed and piloted for this situation. Monoclonal antibodies such as 3F8 are used to “label” receptors (such as GD2) found preferentially on the tumor cells, thereby targeting NB cells for attack by the endogenous immune system. Cis-retinoic acid (cis-RA) is also administered to these patients to encourage immature NB cells to undergo mitotic arrest and either differentiate or die.[6]

Complications of NB include direct cord compression by tumor that extends within the spinal canal. Such intraspinal disease is treated with chemotherapy or surgery to prevent paraparesis.[11]

Opsoclonus-myoclonus syndrome (OMS) is a paraneoplastic syndrome seen in 2–3% of NB patients. It is believed to be immune mediated.[12] OMS is typically treated with corticosteroids, ACTH, and/or intravenous immunoglobulin; second-line, newer treatment approaches include cyclophosphamide and rituximab.[12,13]

Current Conventional Pharmacological Approaches to High-risk NB

General principles of current optimal pharmacotherapy for NB

Pharmacotherapy is most relevant for neuroblastoma patients whose tumors are either too large to permit complete surgical resection or already metastatic at the time of diagnosis.

Drugs are used for several purposes: (1) to ablate tumor cells, in which case effective doses of these drugs may be "targeted" to tumor (e.g., by immunoconjugation) and therefore tolerably toxic to normal tissue or, more frequently, may also ablate normal bone marrow elements, necessitating bone marrow transplantation; (2) to enhance the effectiveness of conventional chemotherapeutic agents against tumor, reduce the toxicity to normal tissues or reduce the necessary dose of radiotherapy to ablate the tumor cells; (3) to "debulk" a very large tumor sufficiently to permit complete surgical resection or, in the case of Stage 4S neuroblastoma, to minimize large tumor-related symptoms while awaiting possible tumor regression; and (4) to prevent recurrence of the tumor presumably by killing or preventing replication of undetectable minimal residual disease after therapy for the initial clinical presentation of the tumor. The discussion that follows looks at the role of pharmacological agents in each of these situations.

Multi-agent chemotherapy

Chemotherapeutic drugs have demonstrated significant success in producing tumor shrinkage and enhancing respectability, as well as increasing event-free survival post-surgery. The primary objectives of induction chemotherapy are to improve surgical resectability by reducing the tumor size in primary and metastatic sites and facilitate complete resection of soft tissue disease, and or induce apparent remission before myeloablative consolidation chemotherapy followed by stem cell transplantation.[14] Induction chemotherapy typically includes dose-intensive cycles of cisplatin and etoposide alternating with vincristine, doxorubicin and cyclophosphamide and, more recently, topotecan. Topotecan (a topoisomerase I inhibitor) and cyclophosphamide are generally used at high dose and according to intensive schedules; their toxicity and feasibility of use are under multicenter study by Children's Oncology Group (COG) for newly diagnosed, high-risk NB.[15] Irinotecan, another topoisomerase I inhibitor, is well tolerated when administered with temozolomide, an alkylating agent, but the efficacy of this combination has not yet been established.

Consolidation regimens vary among protocols but generally aim to produce myeloablation prior to stem cell transplantation. High dose, multi-agent therapy is required. Cis-RA is currently in study as a differentiation-inducing agent administered as prolonged therapy after consolidation.

Refractory or recurrent NB presents considerable challenges. Irinotecan, when combined with cyclophosphamide, has, however, shown significant efficacy and acceptable toxicity when used in relapsed NB. **ABT-751** is an oral tubulin-binding drug with activity against refractory NB; it is still undergoing Phase II trials.[2] Conventional chemotherapeutic agents and other cytotoxic drugs have resulted in significant improvement in event-free survival and relapse rates, however, toxicity is still a significant problem. In order to harness the benefits of chemotherapy, additional adjuvants must be administered to widen the therapeutic index either by diminishing the harmful effects on normal tissues or selectively enhancing the cytotoxic effects on tumors.[16] For example, anti-insulin-like growth factor type I receptor antibody (IMC-A12) is an attractive adjunctive agent that is synergistic with

combination chemotherapy; that is, IMC-A12 enhances the apoptotic response of tumors to conventional treatment.[17]

Radiation therapeutic pharmaceuticals

Radiotherapy is considered to be a vital component of the therapeutic regimen for advanced NB, as NB is a highly radiosensitive tumor. Currently, 21Gy is administered at the primary site where it is used for local control in either fractionated or hyperfractionated regimens.[14] In the case of advanced-stage disease where the tumor is not localized at the primary site and has spread into the surrounding tissue, radiation is used in combination with chemotherapy to improve resectability of the primary tumor. High-dose, inductive chemotherapy followed by complete surgical resection and radiotherapy of 21Gy resulted in a significant reduction in relapse rate and is therefore effective in high-risk NB.

Delivery of radiotherapy selectively to the tumor has been the goal of several innovative radiotherapeutic approaches to NB. Low dose, radioiodinated metaiodobenzylguanidine (MIBG), a norepinephrine analogue taken up by cells like NB cells with a catecholamine transport system, [3] is effective in disease palliation and doses up to 18mCi/kg are tolerable with stem cell support, whereas escalation beyond this dose produces intolerable hematopoietic toxicity.[5]

Although clinical trials using radiotherapy have allowed for a significant improvement in event-free survival in high-risk NB, radiation injury to the growing spine can lead to vertebral damage and scoliosis, consequently radiation is not commonly used in intraspinal tumors. Similarly, since the risks significantly outweigh the potential benefits, radiotherapy is not advised for low-risk tumors even with local residual disease unless progressive deterioration in spite of chemotherapy and surgery is seen.[15] Infants with early stage tumors or 4S NB are not administered radiotherapy because potential acute injury and long-term complications of radiation therapy significantly outweigh the benefits of such treatment.[15,18] A European study is exploring the use of radiotherapy with inductive chemotherapy for newly diagnosed patients and a pilot study by Children's Oncology Group is also underway to understand the benefits and risks of using the carboplatin-etoposide-melphalan inductive chemotherapy with MIBG for ultra-high-risk NB in newly diagnosed patients. One of the common limitations of MIBG is the competition between unlabeled and radiolabeled MIBG which limits its cellular uptake. Ultratrace™ is a no-carrier formulation of I^{131}-MIBG in Phase I clinical trials that is better taken up by tumor cells than I^{131}-MIBG. The use of radiolabeled octreotide with MIBG; conjugation of MIBG with the anti-ganglioside antibody, 3F8; and irinotecan or vorinostat (SAHA), a histone deacetylase inhibitor, as radiosensitizers, in combination with MIBG are also currently being studied.[3] Some highly radiosensitizing chemotherapeutic agents like doxorubicin and actinomycin D exhibit dose-limiting toxicity in combination with radiation; however, cisplatin, topotecan and irinotecan are mild radiosensitizers and safe to give along with radiotherapy.[15]

Total body irradiation (TBI) followed by autologous stem cell transplantation (ASCT) has been shown to decrease disease recurrence in high-risk NB, but has intolerable long-term side-effects in young children.[15] I^{131}-MIBG, when combined with myeloablative

chemotherapy, has been used in patients with chemotherapy-resistant disease and is currently being studied for advanced-stage NB.[5,18–20]

Ablative chemotherapy in stem cell transplantation

Front-line treatment of high-risk NB consolidation includes bone marrow-ablative chemotherapy and TBI or melphalan followed by autologous bone marrow transplantation.[18,19,21] Matthay et al.[19] showed that transplantation of purged autologous bone marrow significantly improves event-free survival compared with intensive chemotherapy.[18] Their subsequent study[22] revealed that TBI-based myeloablative chemotherapy followed by ASCT using bone marrow or peripheral blood stem cells is beneficial in patients that were initially treated with modest doses of induction chemotherapy. Such modest dose induction chemotherapy has also produced encouraging results in clinical trials in which it was followed by I^{131}-MIBG and ASCT.[14,19] Advances in hematopoetic stem cell transplant protocols include infection propylaxis and the use of peripheral blood stem cells (PBSC). There are challenges in the collection, processing and administration of PBSCs but PBSC transplantation provides faster hematopoietic recovery compared to conventional bone marrow transplantation.[15]

Future Chemotherapy in Development

Immunotherapy

Immunotherapy is the concept of “programming” immune cells to act against antigens on cancer cells by labeling cancer cells with monoclonal antibodies. GD2 is a disialoganglioside that is abundantly expressed in NB cells and therefore serves as a good target for immunolabeling.[3,5,14] In normal tissues, GD2 is restricted to central nervous system neurons, which are protected from administered anti-GD2 monoclonal antibodies by the blood brain barrier, and pain fibers in the peripheral nervous system.[14,23] Anti-GD2 antibodies target the GD2 glycolipid and label it to be destroyed by the immune system; their effects can be intensified by cytokines. When surgical resection results in incomplete removal of the tumor, or in the case of recurrent disseminated disease, anti-GD2 immunotherapy with intensive chemotherapy can be effective.[3] Although there are no reports of long-term toxicity as a result of anti-GD2 immunotherapy, acute toxicity, such as pain and allergic reactions, has been reported.[14]

Use in patients of 3F8, a murine antibody to GD2, is hindered by the generation of human anti-mouse antibodies[22] which could be minimized by adjunctively administering high doses of cyclophosphamide.[3] Beta-glucan, a naturally occurring glucose polymer that augments the binding efficiency of anti-GD2 antibodies, [25] is being studied in a clinical trial at Memorial Sloan Kettering Cancer Center, where a combination of oral beta-glucan and murine 3F8 antibody is being administered.[3] Another ongoing clinical trial focuses on comparing patients treated with cis-RA alone to those treated with anti-GD2 antibody plus interleukin-2, granulocyte-macrophage-colony stimulating factor, and cis-RA following high-dose chemotherapy and stem cell transplantation.[3]

Retinoids

Matthay et al. describe the concept of 'maintenance therapy' derived from the observation of relapse in >50% of the patients who appear to be in complete remission after treatment with conventional chemotherapeutics for progressive disease.[3] A natural derivative of vitamin A, RA promotes cell differentiation and growth inhibition. Although in vitro studies using RA as a neoadjuvant therapy were encouraging, acquired resistance resulted in disappointing results in patients with solid tumors.[26] Intracellular retinol is metabolized to all-trans-RA which activates a number of nuclear receptors that heterodimerize and regulate gene transcription.[27]

Synthetic atypical retinoids use different mechanisms and can be used in tumors that are RA-resistant.[28,29] When cis-RA interacts with nuclear retinoid receptors it induces differentiation and inhibits growth in tumor cells by regulating expression of target genes.[3] Cis-RA is currently being used in 3 different clinical trials in combination with chimeric anti-GD2 antibody (Ch14.18), Vorinostat[30] and Zactima (ZD6474), [31] a dual small molecule inhibitor of receptors for vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF).[3] Cis-RA administered following myeloablative chemotherapy improved event-free survival in a Phase III clinical trial.[14] High-dose pulse treatment with 13-cis-RA after transplantation of purged autologous bone marrow has also resulted in improved event-free survival. [18, 22]

Fenretinide is a synthetic analog of RA that produces apoptosis in cancer cells. Unlike conventional retinoids, which bind to nuclear RA receptors and promote gene transcription and consequently differentiation, fenretinide causes apoptosis, possibly by induction of ceramide production and mitochondrial accumulation of reactive oxygen species.[32,33] Fenretinide produces multi-log kill in multiple NB cell lines that are resistant to other retinoids. Fenretinide is currently being tested in Phase II clinical trials.[34] Due to its poor bioavailability fenretinide is currently being studied in intravenous formulations.[14] It is well tolerated and alternative formulations are also being developed for oral administration in young children.[5]

Chemosensitizing agents

Chemotherapeutic resistance is a common challenge in cancer therapy; modulating resistance by administering chemosensitizing agents can help overcome this problem. O^6-benzylguanine is a chemosensitizing agent that circumvents the activity of methylguanine-DNA methyltransferase, a DNA repair protein expressed in NB which confers resistance to the anti-tumor activity of temozolomide. Limited availability of O^6-benzylguanine and increased myelosuppression of this combination makes it less likely to be used in the clinical setting.[3,35] Buthionine sulfoximine, on the other hand, is a selective inhibitor of glutathione synthesis which when administered together with the alkylating agent melphalan, has demonstrated good synergy in the clinical setting. [3]

Novel antimitotic drugs

Antimitotic drugs are a class of chemotherapeutics that inhibit cellular division by interfering with mitotic spindle formation. One conventional antimitotic agent, vincristine, is

an inducer of mitotic arrest. Recent experience with vincristine resistance has given rise to a novel oral anti-mitotic agent, ABT-751.[36] Vincristine works by binding to β-tubulin, while ABT-751 inhibits polymerization of microtubules.[3] MLN8237 is another antimitotic agent which arrests cell growth by inhibiting Aurora A kinase, a protein that is needed for centrosome maturation and spindle formation during mitosis.[37] MLN8237 is currently in Phase I multicenter clinical trials because of its impressive results in preclinical trials in multiple NB models.[38]

Proteasome inhibitors

Proteasome inhibitors synergize with chemotherapeutics and enhance apoptotic response to treatment by interfering with ubiquitin-proteasome degradation of proteins such as p53. Bortezomib is a proteasome inhibitor that induces apoptosis in cancer cells by activating caspases, inhibiting tumor growth and angiogenesis and consequently inducing apoptosis.[39,40] However, studies in a mouse model of metastatic disease showed no complete regressions without regrowth following treatment.[41]

Neurotrophic and growth factor signaling inhibitors

Trk tyrosine kinase receptors are neurotrophin receptors and are highly expressed in NB cells. There are 3 Trk receptors – TrkA, B and C. Upregulated expression of TrkB in NB has been associated with poor prognosis. TrkB-mediated signaling promotes tumor cell survival in high-risk tumors in an autocrine fashion. [42] This makes it a good target and biomarker for NB therapy. CEP-701 (lestaurtinib), a small molecule inhibitor of Trk tyrosine kinase, has a substantial growth inhibitory effect in vivo.[43,44] EGF[45] and platelet-derived growth factor (PDGF) receptor inhibitors like imantinib mesylate are also being studied, as PDGF receptors[46] and/or c-kit[47] expressed in some tumors and thought to be pro-tumor cell survival.

It has been suggested that antagonistic or agonistic ligands of neurotrophin receptors may exhibit synergy with conventional chemotherapeutic agents in NB. Preclinical studies have suggested that both TrkA and the low-affinity nerve growth factor receptor, p75NTR, can be either pro- or anti-apoptotic in neural crest tumors including pheochromocytomas and NB, [48–53] making the adjunctive use of antagonistic or agonistic ligands of these receptors with conventional chemotherapeutic agents problematic.

Sulfhydryl-active strategies

Preclinical studies have also suggested that augmentation of the sulfhydryl content of NB cells, either with adjunctive, exogenous 6-mercaptodopamine or endogenously generated by overexpression of Bcl-2, synergistically enhances the anti-tumor efficacy of enediyne prodrugs in NB.[54–59] However, the toxicity and difficult synthesis and natural product purification of enediynes have generally prohibited their use in the U.S.

Angiogenesis inhibitors

Gastrin-releasing peptide (GRP)[60] and neuropeptide Y (NPY)[61] are secreted by NBs owing to their neuroendocrine origins. GRP induces transcription, expression and secretion of IL-8, a potent angiogenic cytokine which produces increased tumor growth and vascular

density in experimental NB xenografts.[62,63] NPY also stimulates growth of microvascular endothelial cells in vitro causing significant growth and vascularization of NB in vivo.[18,64]

Clinically aggressive tumors tend to be highly vascularized, making angiogenesis an attractive chemotherapeutic target. VEGF expression has been correlated with unfavorable histology and an increase in aggressive behavior in NB.[65,66] This makes VEGF and consequently vascular density important prognostic features that determine the growth of NB tumors.[67,68] Pre-clinical studies of anti-angiogenic molecules have met with varying success in NB models. [5]

Bevacizumab is an anti-VEGF antibody that normalized tumor-associated vasculature in models of NB, reduced blood vessel density and improved intratumoral penetration and efficacy of camptothecans, such as irinotecan; the combination of bevacizumab and irinotecan is now being used in clinical trials. [69]

Bisphosphonate in relation to bone disease and angiogenesis

Bone metastases and progressive degradation of osteoclasts result in mortality in many high-risk NB tumors. Bisphosphonates are a class of drugs that are involved in preventing bone loss. Zoledronic acid (Zometa) is a bisphosphonate which is internalized by osteoclasts and inhibits farnesyl diphosphonate synthase and/or Ras and Rho (GTPase proteins) resulting in apoptosis and a consequent delay in bone metastases. In vivo experiments in mice have shown improved survival and a Children's Oncology Group trial is currently underway in combination with cyclophosphamide.[3]

Nifurtimox (currently in phase II trial)

Nifurtimox is an antiparasitic agent which has been used to treat trypanosomal disease such as Chagas disease. In vitro experiments have shown that nifurtimox has cytotoxic effects against NB, possibly by generating free radicals as it does in parasitic disease. Phase I clinical trials have shown disease stabilization in heavily pretreated patients with relapsed/refractory neuroblastoma treated with nifurtimox alone and in combination with cyclophosphamide and topotecan. Based on these results, nifurtimox is currently being assessed in phase II clinical trials with relapsed/refractory neuroblastoma.[70]

mTOR inhibitors

Mammalian target of rapamycin (mTOR) is a member of the phosphatidylinositol 3-kinase-related kinase family and therefore involved in cell survival, motility and protein synthesis. Rapamycin analogs such as temsirolimus are currently being studied in Phase I trials in patients with recurrent NB and in combination with irinotecan for newly diagnosed patients. Overexpression of insulin-like growth factor (IGF-1R) in many NB tumors is associated with chemotherapeutic resistance. Phase I and II trials are currently underway for the use of IMC-A12 (IGF-1R antibody) as a single-agent as well as in combination with temsirolimus in NB patients. Since mTOR inhibition could activate AKT-mediated survival, AKT inhibitors could present a class of drugs to be administered in combination with temsirolimus in order to enhance its effectiveness in vivo.[3]

Viral therapy

Oncolytic virotherapy has been explored based on the observation that spontaneous viral infections can result in tumor regression. Seneca Valley Virus (NTX-010) is a newly discovered, naturally occurring virus being developed as an oncolytic virus for human cancers. Recent studies by Morton et al. [71] have demonstrated increased cytotoxicity in NB models in vitro and in xenografts in vivo, although further testing and understanding of molecular characteristics are needed.

Engineered herpes simplex virus (HSV)

The use of HSV in treatment of NB is currently being explored in mice with subcutaneous NB xenografts. Oncolytic HSV expressing tissue inhibitor matrix metalloproteinase protein (TIMP3) has resulted in lower tumor burden, and further studies are warranted to understand its activity in combination with current chemotherapeutics.[72] In vitro and in vivo studies using HSV mutant virus NV1066 resulted in increased cytotoxicity relative to saline controls, suggesting its usefulness in local control of unresectable tumors, although its benefits in metastatic disease are yet to be established.[73,74]

Summary and Conclusion

NB remains a challenging therapeutic target, especially when the disease involves large, inoperable primary tumors or metastatic disease. Cytotoxic pharmacologic agents have largely targeted the rapid replication of the tumor cells, rather than their neural or glial characteristics. This has meant that the therapeutic window of chemotherapeutic strategies for neuroblastoma is rather narrow and has led to the development of innovative approaches to better targeting the neuroblastoma cells for attack. Targeted approaches have also been aimed at selective protection of normal cells.

Pharmacotherapy for neuroblastoma is, of necessity, multi-agent, rather than single-agent therapy. As such, drugs have been used not only to kill tumor cells or to protect normal cells from chemotherapy, but also to enhance the effectiveness or decrease the toxicity of radiation therapy and to enhance the likelihood of success and completeness of surgical resection of neuroblastomas.

The future of pharmacotherapy for neuroblastoma lies in using newly developed molecular tools and strategies to better understand and then target for attack those specific characteristics that differentiate tumor from normal and that, in their totality, encompass all tumor cells in a given patient. This is reflective of the fact that while some of the difficulty in treating neuroblastoma lies in the toxicity of such therapies for normal tissue, at least as much of this difficulty results from the heterogeneity of putative target expression in the neuroblastoma cells. Targeting neuroblastomas must therefore include either identification of unifying targets in all of the tumor cells, but none of the normal cells, in a particular patient or development of chemotherapeutic “cocktails” that capture the unique, multifaceted molecular signature of a particular neuroblastoma and differentiate it from normal tissue. Only with this individual tumor- and individual host-focused approach can we hope to preserve the health of the patient while eliminating primary and metastatic tumor and preventing persistence of minimal residual disease.

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Table I

Risk stratification scheme of the Children's Oncology Group[77]

Risk group	INSS Stage	Age at diagnosis	MYCN Amplification status	Ploidy	Histology
Low	1	Any	Any	Any	Any
	2a/2b	Any	Not Amplified	Any	Any
	4S	< 12 months	Not Amplified	DNA Index >1	Favorable
Intermediate	3	< 18 months	Not Amplified	Any	Any
		≥ 18 months	Not Amplified	Any	Favorable
	4	< 12 months	Not Amplified	Any	Any
		12–18 months	Not Amplified	DNA Index >1	Favorable
	4S	< 12 months	Not Amplified	DNA Index = 1	Any
		< 12 months	Not Amplified	Any	Unfavorable
High	2a/2b	Any	Amplified	Any	Any
	3	Any	Amplified	Any	Any
		≥ 18 months	Not Amplified	Any	Unfavorable
	4	< 12 months	Amplified	Any	Any
		12–18 months	Amplified	Any	Any
		12–18 months	Any	DNA Index = 1	Any
		12–18 months	Any	Any	Unfavorable
		≥ 18 months	Any	Any	Any
	4S	< 12 months	Amplified	Any	Any

Table II

Front line therapy for NB based on risk stratification of Children's Oncology Group

Risk Level	Disease Pattern	Treatment	Therapeutic Regimen	5-year Survival (percent)
LOW	Tumor is localized	Allow tumor to safely regress in most cases and surgery to debulk tumors in some cases	Most of these patients do not receive chemotherapy. Recurrent disease, Spinal cord compression or Respiratory compromise/ Hepatic infiltration (4S) - Cisplatin, Etoposide, Doxorubicin and Cyclophosphamide[77]	>98
INTERMEDIATE	Tumor is localized with lymph-node involvement, bone marrow metastases in infants	Moderate-intensity chemotherapy and surgery to debulk tumors	4 (tumors with favorable biological features) to 8 (tumors with unfavorable biological features) cycles each of Carboplatin, Etoposide, Cyclophosphamide, and Doxorubicin	90–95
HIGH	Metastasized tumor to bone and bone marrow (except infants)	Dose intensive induction chemotherapy; Local control with surgery, radiotherapy at the primary tumor site and metastatic sites, Consolidation therapy with myeloablative chemotherapy with ASCT, Minimal residual disease treatment - maintenance therapy with isotretinoin, fenretinide, anti- GD2 immunotherapy and co-administration of GM-CSF	High doses of Cyclophosphamide, ifosfamide, cisplatin, carboplatin, vincristine, doxorubicin, etoposide, and topotecan. Induction with 2 cycles of topotecan and cyclophosphamide or 2 cycles of vincristine, cyclophosphamide, and doxorubicin. Surgical resection of the primary tumor, myeloablative chemotherapy and ASCT	40–50
Special (4S)	Metastasized tumor to liver and skin with minimal bone marrow involvement in infants	Symptomatic treatment including tumor debulking; initial watchful waiting	Low dose chemotherapy and radiation in patients with hepatic involvement and infants <60 days old	>90