Updated Treatment of Neuroblastoma

Jassada Buaboonnam, M.D.

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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Neuroblastoma is the most common extra-cranial tumor in childhood. It is an embryonic malignancy arising from a neural crest of sympathetic ganglion.

Age, stage of disease and molecular defect are important prognostic factors and are used for risk classification and treatment strategy. Approximately 70-80% of patients present with distant metastasis usually bone, liver and bone marrow. Most patients present with symptoms related to tumor growth and metastatic site. Even using high dose chemotherapy followed by autologous bone marrow transplantation less than half of these patients are cured. However, neuroblastoma is one of the rare malignancies which develops spontaneous remission.

The diagnosis is confirmed by microscopic finding and laboratory tests. Neuroblastic tumors histologically present as a small round blue cell tumor and rosette formation. The typical tumor shows small uniform cells with scant cytoplasm. NSE, S100 and chromogranin are usually stained.

Molecular genetics and biology

Neuroblastic tumors usually present with chromosomal and molecular abnormalities and some of these genetic alterations play a major role in prognosis.

The most important biologic marker in neuroblastoma is *MYCN* (locus at 2p24) which is an over expressed oncogene which causes an increased proliferation and rapid tumor progression. The other chromosomal anomalies such as allelic loss at 1p, deletion of the 19q23 are also associated with dismal outcome.

Trk A, Trk B and Trk C are tyrosine kinase which code for a receptor of the NGF family. The increase of Trk A and Trk C expression are correlated inversely with the amplification of *MYCN* which carries a favorable prognosis whereas Trk B over expression is correlated with *MYCN* amplification leading to unfavorable prognosis.

Diagnostic workup

Diagnosis of neuroblastoma is established by demonstrating unequivocally the presence of tumor tissue by histological studies. However, the international consensus accepts a diagnosis made by demonstrating the presence of tumor cells in bone marrow and increase of urine or serum catecholamine metabolites.

CT and MRI are useful to establish the margin of primary tumor and attempt to detect the lymph node metastasis; this data is important for surgery and staging. MRI is superior to CT for characterization of epidural extension as well as identification of leptomeningeal disease. I^{131} MIBG is more sensitive and specific for detection of bony lesion and lymph node metastasis.

Staging and prognostic group classification

The international staging system categorizes patients according to surgical resection accessibility, loco regional lymph node and metastatic site.

In 1999, Shimada et al had developed a histopathologic classification in neuroblastoma. The important feature of classification included the degree of differentiation, the presence of stromal development, cellular proliferation and age at diagnosis. Both the INSS and Shimada classifications are used to determine the treatment strategy in neuroblastoma patients.

Treatment of low-risk neuroblastoma

Patients with low-risk neuroblastoma have a cure rate higher than 90%. The following tumors are categorized as low risk

INSS stage 1 tumors in patients of any age

INSS stage 2A and 2B tumors in infants

INSS stage 2A and 2B tumors in children older than 1 year and in whom the tumor demonstrated either favorable Shimada classification or non amplification of *MYCN*

INSS stage 4S tumors in infants less than 1 year with all favorable biological features low-risk neuroblastoma is generally treated with surgical resection and observation whereas stage 2 low-risk tumors are treated with chemotherapy only if the resectable tumor was less than 50%. Chemotherapy is given for 6 to 24 weeks and consists of moderate doses of carboplatin, cyclophosphamide, doxorubicin, and etoposide. Radiation therapy is reserved patients with a symptomatic life-threatening tumor which does not respond to chemotherapy. The treatment of children with low-risk stage 4S disease depends on clinical presentation - those who are clinically

stable may not require therapy. However, the disease complications, such as respiratory distress from massive hepatomegaly may need a low intensity chemotherapy regimen (low dose cyclophosphamide). Resection of the primary tumor is not associated with improved outcome.

Treatment of intermediate-risk neuroblastoma

Patients with intermediate-risk neuroblastoma generally have a cure rate of 70% to 90%. The following patients are categorized as intermediate risk

1. INSS stage 3 tumors in infants younger than 1 year and in whom the tumor lacks *MYCN* gene amplification.
2. INSS stage 3 tumors in children aged 1 year or older and whom the tumor lacks *MYCN* gene amplification and has a favorable Shimada classification.
3. INSS stage 4 tumors in infants younger than 18 months and in whom the tumor lacks *MYCN* gene amplification.
4. INSS stage 4S tumors in infants younger than 1 year and in whom the tumor lacks *MYCN* gene amplification and has either unfavorable Shimada classification or is near diploid in chromosome number, or both.

Patients classified as intermediate risk with stage 3 tumors with favorable or unfavorable Shimada classification are treated with 12 weeks and 24 weeks of chemotherapy, respectively. In patients classified as intermediate risk with unfavorable biologic features, radiation therapy is given if residual viable tumor remains after 24 weeks of chemotherapy and second-look surgery. Survival of patients with INSS stage 4 disease strongly depends on age-those younger than 1 year have a 5-year disease-free survival rate of 50%-80%. Infants younger than 18 months at diagnosis with INSS stage 4 neuroblastoma who do not have *MYCN* gene amplification are categorized as intermediate risk and are treated with 12 weeks of chemotherapy if the tumor has both favorable Shimada classification and hyperdiploidy but the others are treated with 24 weeks of chemotherapy. Chemotherapy for intermediate-risk patients consists of moderate doses of carboplatin, cyclophophamide, doxorubicin, and etoposide.

Treatment of high-risk neuroblastoma

The following patients are considered to have high-risk neuroblastoma

1. INSS stage 2A/2B tumors in children older than 1 year and in whom the tumor has both unfavorable Shimada classification and *MYCN* gene amplification.
2. INSS stage 3 tumors in infants younger than 1 year and in whom the tumor demonstrates *MYCN* gene amplification.
3. INSS stage 3 tumors in children older than 1 year and in whom the tumor demonstrates either *MYCN* gene amplification or unfavorable Shimada classification.
4. INSS stage 4 tumors in infants younger than 18 months at diagnosis and in whom the tumor demonstrates *MYCN* gene amplification.[1]
5. INSS stage 4 tumors in children older than 18 months with or without *MYCN* gene amplification.
6. INSS stage 4S tumors in infants younger than 1 year at diagnosis and in whom the tumor demonstrates *MYCN* gene amplification.

In children with high-risk neuroblastoma, long-term survival ranges from 10% to 40%. The European Neuroblastoma study group (1982-1985) has shown better results with high-dose therapy with purged autologous hematopoietic stem cell transplantation (HSCT) than three cycles of intensive consolidation chemotherapy (3 year EFS; 34% vs.17%). Another study from Germany also showed the superior outcome of myeloablative therapy. The European study (CCLGNB-1990-11) revealed the superior outcome of rapid sequence induction (10-days cycle) over standard induction (21-day cycle) (10 year EFS; 27% vs. 18%). A phase III trial study in 1991-1996 with two sequential randomizations for 379 neuroblastoma patients was carried out by CCG-3891 which demonstrated improved survival with myeloablative therapy (TBI) and 13-cis retinoic acid. Multi-agent chemotherapy was recommended in high risk patients, including cyclophosphamide, ifosfamide, cisplatin, vincristine, doxorubicin, and etoposide.

After frontline chemotherapy, resection of the primary tumor should be attempted, followed by myeloablative chemotherapy and rescue by stem cell transplantation plus oral 13-cis-retinoic acid for 6 months. The use of radiation therapy for local control after surgical resection is recommended whether or not complete tumor removal was obtained. The novel topoisomerase I inhibitor, Topocetan is frequently used in refractory or relapse neuroblastoma cases. A few randomized studies reveal a 30% overall response rate with 2-year PFS at 36%. In 2005-2007 the current German NB2004 and COG phase III ANBL0532 used topotecan in standard induction protocol with the promising result.

Treatment of recurrent neuroblastoma

The prognosis of recurrent neuroblastoma is usually a dismal outcome. Most recurrent neuroblastoma patients were treated by aggressive chemotherapy with autologous HSCT. The combination of topotecan/cyclophosphamide has been used in recurrent disease; unfortunately the overall response is less than 40%. The MIBG as part of a combination therapy with myeloablative treatment reveal some efficacy especially to alleviate the symptoms, but no statistically significant increase in survival rate.

Novel therapies of neuroblastoma

Currently, MIBG treatment, targeted therapies and immunotherapy are being evaluated in clinical trials of refractory neuroblastoma.

Metaiodobenzylguanidine for therapy of neuroblastoma

MIBG is a guanethidine and norepinephrine derivative which is uptaken by the norepinephrine receptor in the neural crest. MIBG uptake can be shown in the primary site of neuroblastoma and metastatic tumors.

In high risk neuroblastoma patients who are treated by intensive chemotherapy and autologous hematopoietic stem cell transplant long-term survival is still less than 40%, thus stimulating the search for improvement. Iodine-131-MIBG therapy is an attractive addition to current treatment approaches for high risk neuroblastoma. Neuroblastoma is a radiosensitive tumor, and I^{131} MIBG delivers relatively tumor specific radiation

with little impact to normal organs. There are few clinical trials of MIBG treatment in neuroblastoma, mostly in relapse of the disease.

-MIBG as a monotherapy in disease relapse has been conducted in phase II or phase III studies. All patients had previously received extensive chemotherapy, surgery and radiation. The overall response rate was 35-40%.

-MIBG has been used as part of a combined therapy in disease relapse. Multiple trails combining MIBG with myeloablative chemotherapy and autologous stem cell transplantation show a promising response rate with acceptable toxicities.

-MIBG has been used in the treatment of newly diagnosed patients. In Germany, there were 3 clinical trials analyzing the role of MIBG treatment in high risk neuroblastoma patients following induction chemotherapy. Although not statistically significant, the MIBG group had a 3-year EFS 49% compared to 33% in control group.

Targeted therapies

Angiogenesis is a pivotal step in the growth and metastasis of tumors. Vascular endothelial growth factor plays a major role in angiogenesis by binding to their receptors. Bevacizumab (Avastin) is the humanized antibody against VEGF which has been approved as a first-line treatment in colorectal cancer patients. There are few studies of bevacizumab in pediatric malignancies; it seems to have a good safety profile and some antitumor activity in heavily pretreated neuroblastoma patients. However, large multicenter trials are needed to assess the clinical efficacy in neuroblastoma patients.

Immunotherapy

Neuroblastoma presents some antigens recognizable by antibodies but GD2 ganglioside is the most interesting as an antigen because it is expressed in the membrane of the neuroblastoma cell with a very dense pattern and does not lose expression when the cell membrane binds to an antibody. The clinical trails have shown clinical activity in neuroblastoma patients once the MRD phase has been achieved.

CONCLUSION

Despite the prognosis of high risk neuroblastoma is a dismal outcome, the novel treatments such as new stem cell transplantation technique, breakthrough cytotoxic agents and targeted therapy are discovered every year which might be the new hope for neuroblastoma patients.

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