Treatment options for childhood medulloblastoma

Izbor lečenja meduloblastoma kod dece

Marina Nikitović*, Ivana Golubičić*

*Institute for Oncology and Radiology of Serbia, Belgrade, Serbia;
†Faculty of Medicine, University of Belgrade,
Belgrade, Serbia

Key words:
medulloblastoma; radiotherapy; drug therapy;
neurosurgical procedures; child, preschool; treatment outcome.

Introduction

Medulloblastomas, infratentorial or cerebellar, primitive neuroectodermal tumors (PNETs) account for 20% of all childhood brain tumors and 40% of all cerebellar tumors. Peak occurrence is at 4 years of age. Approximately 10% to 15% are diagnosed in infancy and require specific treatment approach. Treatment protocols are based on risk stratification, which takes into account age at presentation, residual disease [residual tumor at the primary site after surgery measured by postoperative gadolinium – enhanced magnetic resonance imaging (MRI)] as well as evidence of disseminated disease at the time of diagnosis. Patients older than 3 years of age with minimal residual disease (if postoperative MRI showed residual disease of 1.5 cm² or less) are classified as an average risk group. Patients are defined as high-risk group if they had metastatic disease at the time of diagnosis (confirmed by gadolinium-enhanced MRI of the head and spine and if lumbar cerebrospinal fluid assessed after resection contained tumor cells); if they had residual disease of more than 1.5 cm² (measured by postoperative gadolinium – enhanced MRI); if they are younger than 3 years of age at the time of diagnosis.

Over the past decades there has been progressive improvement in the results of treatment of this group of patients with overall survival rates higher than 70%.

There are several reasons for this which include advances in neuro-radiological imaging leading to more accurate localization, improvements in neuro-surgical techniques, better perioperative care, improvement in radiotherapy equipment and techniques including greater and more precise dosage delivered to the tumor and refinements in the timing and dosing of chemotherapy.

Treatment options

Surgery

Surgical resection remains the mainstay of therapy with the goal of gross total resection (GTR). All patients who present with a posterior fossa tumor will undergo an open craniotomy. Studies have shown that patients with less then 1.5 cm² residual disease had improved survival. Some patients might require a ventricular shunt or third ventriculostomy prior to resection of the tumor. The majority of patients will have resolution of the hydrocephalus after tumor resection, but approximately 40% will require permanent shunt placement. prognostic factors for permanent shunting are young age, significant pre-surgical hydrocephalus and large tumors.

For most patients, treatment started within 28 days of surgery, the extent of which was defined as: gross total resection if followed by no evidence of residual disease; near-total resection if postoperative MRI showed residual disease of 1.5 cm² or less; and subtotal resection if 25% or more of the tumor remained. The extent of resection is defined by using the neurosurgeons operative notes and by postoperative MRI.

Post-surgical complication characteristically developing after posterior fossa tumor resection is the cerebellar mutism syndrome (CMS) also referred to as the posterior fossa syndrome. This entity typically starts within 1 to 2 days after surgery, persists for weeks to months and consists of paucity of speech leading to mutism, hypotonia, ataxia and emotional instability. In addition, brainstem dysfunction can be seen, including dysphagia, facial weakness and abducens paralysis. In a large study of 450 children, CMS developed after surgery in 107 (24%). Only brainstem involvement was predictive for the development of CMS. Another series analyzed 253 children in which CMS developed in 20 children.
All of these cases had brainstem involvement. Evidence of hydrocephalus also appears to exacerbate the development of CMS. Individual case studies report on successful use of dopamine agonists, such as bromocriptine, for the treatment of CMS but unfortunately children are often left with dystrophic speech. Therefore, careful resection is recommended, especially in children with brainstem involvement.

Radiation therapy

Radiation therapy was the first adjuvant treatment for brain tumors and was initially applied to the treatment of adult gliomas and pituitary tumors in the early 1900s. It remains very effective therapy for many malignant pediatric brain tumors, contributing substantially to duration of survival and the chance of cure.

Medulloblastomas are very radiosensitive tumors and adjuvant therapy with radiation has been the standard of care in children older than 3 years of age. The reported, long-term side effects of radiation therapy, such as hearing loss, cognitive decline, endocrine abnormalities, vascular complications, as well as secondary malignancies have inspired many investigators over the years to try to reduce the radiation dose as well as the radiation field. The Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) now known as the Children’s Oncology Group (COG) compared in a prospective trial (POG 631/COG 923) reduced neuroaxis radiation of 23.6 Gy to the standard regimen of 36 Gy with equal posterior fossa radiation (54 Gy) for children with average risk medulloblastoma. The interim analysis indicated an increased risk of early relapse with reduced radiation. Since then, many studies have focused on the introduction of chemotherapy to reduce radiation dose but maintain adequate survival.

The introduction of conformal radiotherapy enabled radiation oncologists to reduce the radiation field. In previous treatment strategies after craniospinal irradiation boost radiotherapy was delivered to the complete posterior fossa. Currently, most investigators used a boost dose to the tumor bed, instead of irradiating the entire posterior fossa using conformal radiation therapy with 5-year overall survival rates of 84% for an average risk-group of patients.

Proton beam therapy is another alternative to conventional radiation therapy. The benefit of using proton beams is the higher proportion of tumor versus normal tissue distribution. Proton beam therapy is not currently used in Serbia.

Radiosurgery can successfully be used for local tumor control in patients with recurrent or residual disease. However, stereotactic radiation as primary treatment modality is limited given the propensity of medulloblastomas for dissemination and treatment failure can occur due to subclinical craniospinal metastases.

The current standard for average risk medulloblastoma includes postoperative craniospinal irradiation of 23.4 Gy, plus a boost to the posterior fossa of 54 Gy followed by 12 months of chemotherapy. This regimen has resulted in a 5-year overall survival rates of 80% or better. In high-risk disease, 36 Gy craniospinal irradiation, plus a boost at the posterior fossa of 54 Gy, followed by chemotherapy is standard. Ongoing trials are investigating the benefit of chemotherapy during irradiation.

Chemotherapy

There has been a progressive improvement in the results of treatment of children with medulloblastoma with overall survival rates of 70% or better.

Reducing the radiation dose without adding chemotherapy has led to worse outcomes in children with medulloblastoma. Many studies have investigated the role of chemotherapy in addition to radiotherapy with the goal to reduce the amount of radiation. Different chemotherapeutic agents has been used and are now standard in the management of children with medulloblastoma in all risk groups. Alkylators and platinum compounds such as lomustine, cyclophosphamide and cisplatin remain key therapeutic agents. Vincristine is often administered weekly during radiotherapy and as adjuvant chemotherapy. Children with average risk disease, who were treated with craniospinal radiotherapy of 23.4 Gy and 55.8 Gy to the posterior fossa, and adjuvant chemotherapy (lomustine, vincristine and cisplatin) showed a progression-free survival (PFS) of 86% at 3 year and 79% at 5 years. The European Hintumor (HIT) 91 trial compared outcome in patients with average risk medulloblastoma receiving either neoadjuvant chemotherapy (prior to radiation therapy) or postradiation chemotherapy. The 5-year PFS in the postradiation chemotherapy arm was 78% and in the neoadjuvant chemotherapy arm was 65%.

These and some other studies confirm the benefit of adjuvant chemotherapy for the treatment of average risk medulloblastoma and regimen reported by Packer and Packer et al. as previously described remains the standard of therapy for average-risk medulloblastoma patients.

For high-risk medulloblastoma patients, the priority remains to improve survival. Average event-free survival (EFS) at 5 years for high-risk medulloblastoma ranges from 34% to 40% across studies. Multiple studies have used different chemotherapy protocols, including neoadjuvant chemotherapy in combination with surgery and radiation to improve survival with moderate success. The use of prolonged neoadjuvant chemotherapy resulted in inferior outcomes compared with those obtained with shorter times between surgery and radiation therapy. The best outcome for high-risk medulloblastoma patients to date was achieved by craniospinal irradiation (36 Gy M0-1; 39.6 Gy M2-3) with a boost to the primary tumor site after maximal surgical resection followed by dose-intensive cyclophosphamide, vincristine and cisplatin chemotherapy with autologous peripheral blood stem rescue. The 5-year EFS was 70%. The COG (COG 99701) treated 57 patients with metastatic medulloblastoma with vincristine and carboplatin while receiving radiation therapy (36 Gy for craniospinal irradiation), followed by monthly treatment with cyclophosphamide and vincristine. The 4-year OS and EFS were reported at 81% and 66%, respectively.

All these studies indicate that chemotherapy is pivotal for the treatment of high-risk medulloblastoma patients and ongoing studies are investigating the best regimen for these patients.

Treatment for children less than 3 years of age

Small children with medulloblastoma have poorer survival than older children when treated with standard radiotherapy and even more significantly they sustain much greater treatment-related neurotoxicity. Also, it is believed that medulloblastoma in a very young child have a more aggressive behavior and a higher incidence of metastasis at the time of diagnosis, although the data is limited. Evans at al. reported that 34% of children under the age of 4 years presented with disseminated disease compared with only 14% of children aged 4 years or older. Similar results were reported separately with 62% of children less than 5 years of age demonstrating metastatic disease versus 38% in children older than 5 years of age.

The impact of age on prognosis is difficult to assess because younger patients normally receive different treatment modalities than older children. In an attempt to delay or obviate radiation therapy, multiple studies have been performed using different chemotherapy regimens.

In the mid 1980s, the POG conducted a trial (referred to as Baby-POG I) enrolling 102 children less than 3 years of age with brain tumors in which prolonged postoperative chemotherapy was given with an attempt to delay radiation therapy. The 5-year PFS of 62 children with medulloblastoma less than 3 years of age was reported at 31.8% and the 5-year OS at 39.7% using a combination of cyclophosphamide, vincristine, cis-platinum and etoposide. Radiation was delayed until 3 years of age. The main predictor for survival was extent of surgical resection. Twenty children undergoing GTR had a 5-year OS of 60% compared with 33 children who had subtotal resection and who had a 5-year OS of 32%.

Other studies investigated a similar approach. The CCG used the “8-in-one-day” regimen followed by either radiation after two cycles of chemotherapy versus craniospinal irradiation 1 year after diagnosis and completion of maintenance chemotherapy. Forty-six children with medulloblastoma were less than 18 months old with 3-year PFS of 22%. Thirty percent were alive and disease-free at a mean follow-up of 72 months. The poorer outcome in the “8-in-one-day” regimen is probably best explained by the less intensive chemotherapy regimen in this study compared to the Baby-POG I trial.

Also because of concern for neurotoxicity of radiotherapy in young children, the use of high-dose ablative chemotherapy with autologous bone marrow transplant or stem cell rescue for children with recurrent or newly diagnosed tumor is being explored. In view of the chemo-sensitivity of medulloblastoma there have been preliminary studies in which a small number of newly-diagnosed infants were successfully treated in consolidation with high-dose chemotherapy supported by autologous peripheral stem cell rescue; this approach may have a larger role in treating young children, as it may for patients who relapse after standard therapy.

Investigational therapy

Better therapy for medulloblastoma undoubtedly will have its basis in clarification of tumor molecular biology. Improved understanding of the molecular signature of individual tumors will help in determining prognosis and more accurate tumor risk-stratification, permitting children at lower risk for recurrence to safety receive less toxic therapy and reserving more intensive treatment for those at higher risk. Knowledge of the molecular defects critical in tumorigenesis could also provide the means to use them as targets for novel therapeutic approaches.

A number of studies have identified several possible molecular traits that could serve as prognostic factors, as well as potential targets for therapy of medulloblastoma. Among these are the amplification or overexpression of several oncoproteins, including epidermal growth factor receptor B2 (ERBB2), C-Myc, and N-Myc, loss of caspase-8 expression, and mutations in several other signal transduction pathways including the PTCH1/“Sonic Hedgehog” pathway, “Wingless” (WNT/WG)/beta catenin pathway and platelet-derived growth factor-alpha (PDGF-a) and RAS/MAP tyrosine kinase pathway.

Understanding mechanisms of tumorigenesis for future molecular classification and prognosis is also the first step in the development of molecular-targeted therapies. Specific small molecule tyrosine kinase inhibitors could prove effective against targets in some medulloblastoma (and other brain tumors). These include imatinib mesylate (Gleevec), a PDGFα/RAS/MAP tyrosine kinase inhibitor, Erlotinib (Tarceva), which inhibits the oncogene, ERBB2 tyrosine kinase and Iressa (gefitinib), which inhibits the epidermal growth factor receptors (EGFR) tyrosin kinase. Some of these agents are tested in ongoing clinical trials.

The retinoid, cis-retinoic acid, is another therapeutic agent soon to be evaluated in a randomized fashion in the upcoming COG protocol for high-risk medulloblastoma/PNET tumors. Retinoids mediate apoptosis in medulloblastoma cells in vitro, and suppres tumor growth in xenograft models.

Conclusion

Childhood medulloblastomas remain a challenging oncologic condition.

The main goal for patients with average-risk disease is to improve morbidity of current treatment regimens and maintain adequate survival. For patients with high-risk and recurrent disease, survival remains poor; therefore, improving outcome is the focus of current investigations. Advances in understanding molecular profile and associated clinical outcome will eventually lead to better risk stratification and enable neuro-oncologist to better determine risk-benefit profiles for each individual patient. Therapy for childhood medulloblastoma requires a delicate balance between the need to intensify therapy for some group of patients and the desire to reduce potentially neurotoxic therapy and risk for other malignancies, so as to have greater number of survivors with cognitive, psychological and endocrinologic abilities allowing them to have a better quality of life.


Received on December 8, 2011.
Revised on March 22, 2012.
Accepted on March 26, 2012.