Childhood Brain Tumors

The therapy of infantile malignant brain tumors: current status?

Chantal Kalifa and Jacques Grill
Pediatric Department, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805, Villejuif cédex, France

Key words: atypical teratoid rhabdoid tumors, brain tumors, chemotherapy, choroid plexus carcinomas, ependymomas, infants, malignant gliomas, medulloblastomas, sequelae

Summary

Malignant brain tumors are not uncommon in infants as their occurrence before the age of three represents 20–25% of all malignant brain tumors in childhood [1]. Genetic predisposition to infantile malignant brain tumors are known in Gorlin syndrom for example who present with desmoplastic medulloblastoma in about 5% of the affected patients. In addition, sequelae from tumor and its treatment are more severe at this age [2]. Thus, malignant brain tumors represent a true therapeutic challenge in neuro-oncology. Before the era of modern imaging and modern neurosurgery these malignant brain tumors were misdiagnosed or could not benefit of the surgical procedures as well as older children because of increased risks in this age group. Since the end of the 80s, noninvasive imaging procedures produce accurate diagnosis of brain tumors and improvement in neurosurgery, neuroanesthesia and perioperative intensive care permit safe tumor resections or at least biopsies. Consequently, the pediatric oncologists are more often confronted with very young children who need a complementary treatment.

Before the development of specific approaches for this age group, these children received the same kind of treatment than the older children did, but their survival and quality of life were significantly worse. The reasons of these poor results were probably due in part to the fear of late effects induced by radiation therapy, leading to decrease the necessary doses of irradiation which increased treatment failures without avoiding treatment related complications [3].

At the end of the 80s, pilot studies were performed using postoperative chemotherapy in young medulloblastoma patients. Van Eys treated 12 selected children with medulloblastoma with MOPP regimen and without irradiation; 8 of them were reported to be long term survivors [4]. Subsequently, the pediatric oncology cooperative groups studies have designed therapeutic trials for very young children with malignant brain tumors. Different approaches have been explored:

- Prolonged postoperative chemotherapy and delayed irradiation as designed in the POG (Pediatric Oncology Goup).
- Postoperative chemotherapy without irradiation in the SFOP (Société Française d’Oncologie Pédiatrique) and in the GPO (German Pediatric Oncology) studies.
- The role of high-dose chemotherapy with autologous stem cells transplantation was explored in different ways:
  - High-dose chemotherapy given in all patients as proposed in the Head Start protocol
  - High-dose chemotherapy given in relapsing patients as salvage treatment in the French strategy

In the earliest trials, the same therapy was applied to all histological types of malignant brain tumors and whatever the initial extension of the disease. This attitude was justified by the complexity of the classification of all brain tumors that has evolved over the past few decades leading to discrepancy between the diagnosis of different pathologists for a same tumor specimen. Furthermore, it has become increasingly obvious that the biology of brain tumors in very young children is different from that seen in older children. However, in the analysis of these trials an effort was made to give the results for each histological groups, according to the WHO classification and after a central review of the tumor specimens.

All these collected data have brought to an increased knowledge of infantile malignant brain tumors in terms of diagnosis, prognostic factors and response to chemotherapy. Furthermore a large effort was made to study long term side effects as endocrinopathies, cognitive deficits, cosmetic alterations and finally quality of life in long term survivors. Prospective study of sequelae can bring information on the impact of the different factors as hydrocephalus, location of the tumor, surgical complications, chemotherapy toxicity and irradiation modalities. With these informations it is now possible to design therapeutic trials devoted to each histological types, adapted to pronostic factors and more accurate treatment to decrease long term sequelae.

Medulloblastoma/PNET

The introduction of chemotherapy in patients with medulloblastomas is currently changing the philosophy of their treatment. The first publication of the Baby POG 1 study is considered as a milestone paper for the
treatment of brain tumors in children <3 years [5]. In this trial the most common tumors were medulloblastomas. Sixty-two children were treated with postoperative chemotherapy and delayed craniospinal irradiation performed after the age of 3. The 5-year PFS is 31.8 ± 8.3% and the 5-year overall survival is 39.7 ± 6.9%. Depending on the age at diagnosis, the delay in radiation of 1 or 2 years had no impact on survival. The strongest prognostic factor was the quality of the surgical resection: the 5-year survival was 60% for the 20 children who had a gross total resection and 32% for the 33 children who had an incomplete resection. The 5-year survival of the 13 patients who had a gross total resection and no metastases at diagnosis was 69%. Most of the failures occurred during the first 6 months of chemotherapy with no progressive disease occurring after 2 years of therapy [6].

A following study comparing the Baby POG 1 dose regimen with a moderately dose-intensiﬁed version of the same regimen has been conducted. Preliminary results suggest no advantage for dose intensiﬁcation (Strother personal communication).

Forty-six children less than 18 months have been involved in the CCG study of postoperative chemotherapy «eight drugs in 1 day» regimen and proposed delayed irradiation. The 3-year PFS was 22 ± 6% (30% for those with gross total resection and no metastasis) but most the patients who had prolonged survivals did not receive irradiation following completion of chemotherapy [7].

A different approach have been taken in a pilot study from Philadelphia: 10 children 18–60 months of age with localized medulloblastoma received a reduced dose radiation therapy with 18 Gy to the craniospinal axis, a dose of 50.40–55.80 Gy to the posterior fossa and a chemotherapy consisting of weekly vincristine during irradiation and 8 cycles delivered every 6 weeks of the combination of vincristine, cisplatin, CCNU. There were 7 survivors and the overall survival at 6 years is 70 ± 20% [8].

Others groups have attempted to eliminate radiation in young medulloblastoma patients. The first report was those of 12 medulloblastoma patients <3 years treated from 1976 to 1988 with postoperative MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone); 8 of them are long term survivors and 6 of these 8 patients did not receive radiation [9].

The Australian New Zealand Childhood Cancer Group treated 16 medulloblastoma patients with a combination of cyclophosphamide, vincristine etoposide; with a median follow-up of 25 months, 7 remained alive, none of them having received irradiation [10].

In the first German study SKK87 for medulloblastoma patients <3 years postoperative chemotherapy comprised procarbazine, ifosfamide, etoposide, high dose methotrexate and delayed irradiation; the 5-year survival rate was 50% in 30 children (Kuehl personal communication). In the HIT SKK 92 (which included high risk as well as standard risk patients), radiation was eliminated in children without evidence of disease after chemotherapy which consisted in cyclophosphamide, carboplatin, vincristine, etoposide, intravenous high dose (5 g/m²) and intraventricular methotrexate; 45 of 62 eligible patients were treated according to the protocol and the 5-year PFS and OS were 55.5 ± 7.7% and 63.3 ± 7.4% respectively. Eleven of 18 patients without postoperative residual tumor and without metastasis remained in CCR (PFS 77.8 ± 9.8%). In 14 patients with postoperative residue but no metastases the 5-year PFS and OS are 50 ± 13.4% and 56.3 ± 13.5%. PFS and OS were lower in M2–M3 patients (30.7 ± 12.8% and 34.6 ± 14.4%). In this study a correlation was found between the cumulative dose of intraventricular methotrexate and the risk of leukencephalopathy (Rutkowski personal communication).

In the ‘Head Start I’ protocol, medulloblastoma patients received postoperative chemotherapy with vincristine, cisplatin, etoposide, cyclophosphamide and a high dose combination of carboplatin, etoposide and thiopeta with stem cells rescue; no irradiation was performed if the patients were in remission at the end of treatment. The 2-year EFS of the 12 medulloblastoma patients <3 years who entered this study was 38% [11].

The ‘Head Start II’ protocol was designed for patients presenting with leptomeningeal dissemination; the postoperative regimen was intensified with high-dose methotrexate. The complete response rate observed in 21 medulloblastoma patients was 81%. The 3-year EFS was 49% (95% CI, 27–72%) [12].

The French BB-SFOP protocol was designed to deliver prolonged postoperative chemotherapy in young children with a malignant brain tumor and to avoid radiation therapy. Chemotherapy was given in alternating cycles of carboplatin and procarbazine, etoposide and cisplatin and vincristine and cyclophosphamide, over 16 months. No irradiation was given in patients unless they relapsed. In case of local progressive or recurrent disease, the recommended salvage treatment was high-dose busulfan (600 mg/m²) and thiopeta (900 mg/m²) with autologous stem cell support, followed by irradiation limited to the site of disease at the time of progression [13]. In 1995 the protocol was modified for high-risk patients. All patients with a postoperative local residue received the high-dose busulfan-thiopeta combination with autologous stem cells transplant followed by 50 Gy irradiation limited to the posterior fossa. Medulloblastoma patients with a leptomeningeal dissemination at diagnosis were enrolled into a repeated high-dose chemotherapy strategy (two courses of melphalan 100 mg/m² and one course of busulfan (480–600 mg/m²) and thiopeta (720–900 mg/m²); autologous peripheral blood stem cells transplant were performed after these three courses). Radiation therapy was administered at the dose of 50 Gy on the primary tumor bed (and not on the cranial axis).

Eighty medulloblastoma patients have entered the BB-SFOP study. Fifty-eight patients have relapsed and 39/58 have received the salvage treatment using high-dose busulfan-thiopeta and irradiation to the site of disease (5 of the metastatic patients, 12 of the patients with a post operative residue, 22 of the standard-risk patients). Four patients have received the sequential high-dose chemotherapy regimen at the time of a metastatic relapse.