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## Original Paper

# Etoposide and Thiotepa Followed by ABMT (Autologous Bone Marrow Transplantation) in Children and Young Adults with High-grade Gliomas

E. Bouffet,[1] C. Mottolese,[2] A. Jouvet,[3] I. Philip,[4] D. Frappaz,[1] C. Carrie[5] and M. Brunat-Mentigny[1]

[1]Paediatric Department, Centre Léon Bérard, 28 rue Laennec, 69373 Lyon Cedex 08; [2]Department of Paediatric Neurosurgery, Hôpital Wertheimer, Lyon; [3] Department of Neuropathology, Hôpital Wertheimer, Lyon; [4]Department of Intensive Chemotherapy and Bone Marrow Transplantation, Centre Léon Bérard, Lyon; and [5]Department of Radiotherapy, Centre Léon Bérard, Lyon, France

**The addition of conventional chemotherapy to irradiation has improved the outcome of children with malignant gliomas. The application of high-dose chemotherapy has been proposed as a possible way to increase the response rate and thus the survival in children with malignant brain tumours. High-dose etoposide (500 mg/m$^2$/day × 3) and thiotepa (300 mg/m$^2$/day × 3) followed by bone marrow transplantation were given to 22 patients (age range 4–20 years) with newly diagnosed or recurrent high-grade glioma. The response rate in the 14 assessable patients was 29% with one complete and three partial responses. 5 patients had stable disease, and 5 progressive disease. 2 patients died of treatment-related toxicity. Only 3 patients remain alive disease free 54, 60 and 65 months after high-dose therapy. For children with high-grade gliomas, survival using high-dose chemotherapy is no better than that reported with conventional treatments.** © **1997 Elsevier Science Ltd. All rights reserved.**

**Key words: malignant glioma, child, chemotherapy, bone marrow transplantation**

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## INTRODUCTION

BRAIN TUMOURS constitute almost 25% of childhood neoplasms. Malignant brain tumours in childhood are known to have a better outcome than in adults. Disease-free survival for the most frequent, medulloblastomas and ependymomas ranges from 40 to 70% [1]. The prognosis of high-grade gliomas is, however, poorer depending upon the localisation. Up to 30% of children with supratentorial gliomas will remain disease-free at 3 years, while 2-year survival is unusual for children with intrinsic diffuse brain stem gliomas [2, 3]. Furthermore, the use of high-dose radiation therapy given to extended fields within the central nervous system leads to major sequelae such as compromised growth and mental development [4]. In newly-diagnosed children with high-grade gliomas, the use of chemotherapy has become standard, due to the result of the randomised trial of the Childen's Cancer Study group [5]. However, the prognosis of these patients remains poor, and high-dose chemotherapy has been proposed to improve the therapeutic index. The objectives of high-dose chemotherapy in children with brain tumours are to increase survival rate and to delay—or even to avoid—radiation therapy. Several studies have been conducted over the last 5 years [6–10]. We report here a single institution experience of high-dose etoposide and thiotepa followed by autologous bone marrow transplantation (ABMT) in 22 children and young adults with high-grade gliomas.

Correspondence to Eric Bouffet, Institute of Child Health, Bristol Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ, U.K.
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## PATIENTS AND METHODS

*Eligibility criteria*

Patients aged 20 years or less with newly diagnosed, recurrent or refractory high-grade (WHO grade III or IV) glioma and diffuse infiltrating brain stem glioma were eligible for the study. All patients or legal guardians gave

*Table 1. Treatment plan*

| Day | Preparation | Ancillary drugs |
|---|---|---|
| −5 | Etoposide 500 mg/m$^2$ i.v. | Clonazapam 0.1 mg/kg/day in continuous infusion until |
| | Thiotepa 300 mg/m$^2$ i.v. | ↓ |
| −4 | Etoposide 500 mg/m$^2$ i.v. | |
| | Thiotepa 300 mg/m$^2$ i.v. | |
| −3 | Etoposide 500 mg/m$^2$ i.v. | |
| | Thiotepa 300 mg/m$^2$ i.v. | |
| −2 | Rest | ↓ |
| −1 | Rest | day 0 |
| 0 | Autologous bone marrow infusion | Parenteral Nutrition |

informed consent prior to study entry. The study was approved by the local institutional review board.

*Chemotherapy regimen (Table 1)*

Bone marrow was harvested for cryopreservation prior to chemotherapy. 2 patients had peripheral stem cell harvest. Etoposide was administered for 3 consecutive days as a 2-h i.v. infusion at a dose of 500 mg/m$^2$/day. Thiotepa was infused 1 h later over 1 h, at a dose of 300 mg/m$^2$/day. The regimen was administered on days −5, −4 and −3 with autologous bone marrow reinfusion on day 0. Intravenous clonazepam was given 0.1 mg/kg/day as a continuous infusion from day −5 to day 0 to prevent thiotepa-related seizures. Following bone marrow transplantation (BMT), patients were either treated in laminar air flow rooms or in conventional cubicles. They received parenteral alimentation and broad spectrum antibiotics if required. Blood cell transfusions were given to maintain a haemoglobin level over 8 g/dl, and platelet transfusions were given to maintain a platelet count above $50 \times 10^9$/l. All blood products were irradiated.

*Evaluation of the response*

Response was evaluated 30 days following BMT. Assessment of the response was based upon CT (computer tomography) or MRI (magnetic resonance imaging) scans, corticosteroid requirements and by neurological evaluation. Radiological evaluation took into account the volume of the tumour and the peritumoral oedema, the presence and the extent of contrast enhancement. Complete response (CR) was defined as a disappearance of all visible tumour, no steroid requirement, increased or stable Karnofsky scale, and neurologically stable or improved. Partial response (PR) was defined as >50% decrease in tumour size, corticosteroid dose stable or reduced, increased or stable Karnofsky scale, neurologically stable or improved. Progressive disease (PD) was defined as >25% increase in tumour size or any new tumour on any following scan, corticosteroid dose stable or

*Table 2. Patients' characteristics*

| Patient | Sex/age | Location | Grade | Previous therapy | Status before VP-TT | Response to VP-TT | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | F/7 | Gliomatosis | NA | Biopsy-CT | PR1 | NE | TD 23 days |
| 2 | F/12 | Gliomatosis | IV | Biopsy-XRT | PD (rel) | PD | DOD 1.5 mo |
| 3 | M/12 | Corpus callosum | III | Biopsy-XRT | PR1 | SD | DOD 5 mo |
| 4 | M/4 | Thalamus | III | Biopsy-XRT | SD | SD | APF 65 mo |
| 5 | M/10 | Thalamus | III | Biopsy-XRT | PD (rel) | PD | DOD 3 mo |
| 6 | M/17 | Occipital | III | GTR-XRT | CR1 | CCR | DOD 11 mo |
| 7 | M/9 | Parietal | IV | GTR-XRT | CR1 | CCR | DOD 6 mo |
| 8 | M/19 | Temporal | OA | GTR-XRT | CR1 | CCR | DOD 23 mo |
| 9 | M/20 | Parietal | OA | GTR-XRT | CR1 | CCR | DOD 19 mo |
| 10 | F/9 | Occipital | OA | GTR-XRT | CR1 | CCR | DOD 9 mo |
| 11 | F/19 | Temporal | IV | Part Surg-CT | PR1 | SD | DOD 18 mo |
| 12 | F/5 | Brain stem | III | Part Surg-XRT | PR1 | PR | APF 60 mo |
| 13 | M/15 | Frontal | III | Part Surg-XRT | PR1 | PR | DOD 14 mo |
| 14 | M/7 | Brain stem | III | Part Surg-XRT | SD | SD | DOD 9 mo |
| 15 | F/14 | Spinal cord | IV | Part Surg-XRT | PD (rel) | PD | TD 15 days |
| 16 | M/20 | Frontal | IV | Part Surg-XRT | PD (rel) | PD | DOD 1.5 mo |
| 17 | M/6 | Occipital | OA | Part Surg-XRT | PR1 | CR | APF 54 mo |
| 18 | F/9 | Temporal | III | Surg (×2)-XRT-CT | CR2 (rel) | CCR | DOD 4 mo |
| 19 | F/8 | Temporal | OA | Surg (×2)-XRT-CT | CR2 (rel) | CCR | DOD 4 mo |
| 20 | M/5 | Spinal cord | IV | Surg (×3)-XRT-CT | PD (rel) | PD | DOD 2 mo |
| 21 | F/11 | Brain stem | NA | CT-XRT | PD (rel) | PR | DOD 4 mo |
| 22 | F/10 | Brain stem | NA | CT-XRT | PD (rel) | SD | DOD 6 mo |

VP-TT, high-dose etoposide and thiotepa; M, male; F, female; NA, non-available; OA, anaplastic oligoastrocytoma; XRT, radiotherapy; CT, chemotherapy; GTR, gross total removal; Part Surg, partial surgery; PR1, first partial remission; CR1, first complete remission; CR2, second complete remission; Rel, relapse; PD, progressive disease; SD, stable disease; CR, complete response; PR, partial response; NE, non-evaluable; CCR, continuous complete remission; DOD, dead of disease; TD, toxic death; APF, alive progression-free.

increased, decreased or stable Karnofsky scale and neurologically stable or worse. Stable disease (SD) applied to all other situations.

*Patient characteristics*

Table 2 presents the clinical characteristics, responses and outcome of 22 patients enrolled on this study between December 1989 and July 1993. There were 12 boys and 10 girls. Patients ranged in age from 4 to 20 years. There were 7 patients with anaplastic astrocytoma, 5 with anaplastic oligodendroglioma or oligoastrocytoma, 3 with supratentorial glioblastoma, 3 with brain stem glioma, 2 with spinal cord glioblastoma and 2 with diffuse gliomatosis. 20 patients had previous surgery, 20 radiotherapy and 7 chemotherapy. 11 patients received high-dose therapy as a part of their initial schedule, 2–3 months after completion of radiation therapy. 2 other newly-diagnosed patients were intensified after surgery and nitrosourea-containing chemotherapy. 9 were enrolled at time of relapse. 15 patients had measurable disease. In 5 newly diagnosed and 2 relapsing patients, the resection was intended to be complete. Karnofsky scale ranged from 40 to 100% (median 80%), and 8 patients were on steroids due to neurological impairment or symptoms of increased cranial pressure.

## RESULTS

2 patients died of toxicity before response evaluation. One was obviously a non-responder and has been included in the PD group. The other one died of diffuse interstitial pneumonitis without any symptoms of tumour progression. She was considered as non-evaluable.

The overall response rate to high-dose chemotherapy was 29%. Among the 14 evaluable patients with measurable disease, there was one complete and 3 partial responses (Figure 1). All patients treated in first or second remission remained disease-free at time of evaluation. 5 patients had stable disease and 5 progressed. Haematological toxicity was severe with all patients having an absolute neutrophil count $<0.5 \times 10^9$/l for a median 23 days (range 14–38 days). Median time to recovery of platelets to $\geqslant 50 \times 10^9$/l was 30 days (range 17–55 days). All patients required RBC and platelet support.

All patients experienced grade I to III gastro-intestinal toxicity during chemotherapy. 14 developed thiotepa-related cutaneous toxicity with erythematous rash and subsequent desquamation with prolonged hyperpigmentation. Mucositis was severe in all patients and required i.v. morphine for 3–12 days (median 8 days). Early neurotoxicity was observed in 11 patients. Events included severe headache in 7, drowsiness in 5 patients, hallucinations in 3, seizures in one and intracranial haemorrhage in one. In 7 cases, a CT scan was performed to exclude tumour progression. Increased peritumoral oedema was observed in 4 patients, and intracranial haemorrhage in one. All these symptoms were transient and resolved within 2 weeks.

All patients developed febrile episodes while neutropenic and received broad-spectrum antibiotics, acyclovir and amphotericin. The median duration of fever was 9 days (range 1–19 days). There were 4 documented septicaemic episodes (two *Staphylococcus epidermidis*, one *Streptococcus mitis* and one *Pseudomonas maltophila*). The patient with pseudomonas sepsis died of multiple organ failure. 3

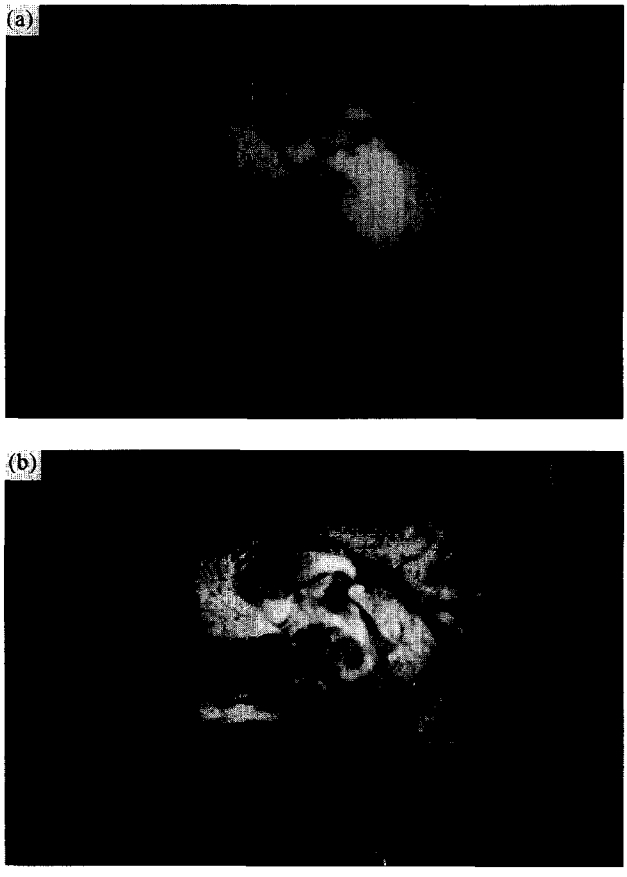


**Figure 1. (a) Post contrast $T_1$ weighted MRI scan. A large infiltrating diffuse pontine lesion. Chemotherapy was initiated in a child with tetraparesis necessitating high-dose steroids 160 mg/day. (b) Post contrast $T_1$ weighted MRI scan 1 month after bone marrow transplantation shows a partial response. The child improved clinically and steroids were decreased to 20 mg/day.**

patients developed localised pulmonary infection, and one diffuse interstitial pneumonitis. Since the onset of this pneumonitis occurred early after high-dose therapy (day 0 of bone marrow transplantation), this complication was more likely due to BCNU lung in a previously heavily treated child than to the high-dose regimen. Broncho-alveolar lavage did not sow evidence of an infectious process. Post mortem examination showed diffuse alveolar damage with lung fibrosis. No organism was isolated in this specimen and bacterial, fungal and viral cultures were negative.

Apart from the child with multiple organ failure, no cardiac, hepatic or renal complications occurred.

*Survival*

One patient received additional radiation therapy, 2 months following BMT. The median survival and progression-free interval are 9 months (range 1–65+) and 5 months (0–65+), respectively. 3 patients are alive progression-free 54, 60 and 65 months after BMT. 2 had grade III astrocytomas, and one an anaplastic oligodendroglioma. 2 were responders (one CR and one PR) and one had stable disease following high-dose chemotherapy. The residual lesion remained unchanged in the patient with stable disease. It disappeared within 2 years in the patient who showed a partial response. These 3 long-term survivors have mild to moderate disabilities. One suffers hearing loss. 2

developed seizure disorders that started 32 and 34 months after diagnosis. They all have schooling difficulties that require special education programmes.

19 patients died: 2 from chemotherapy related toxicity, and 17 from progressive or recurrent disease. 13 patients recurred locally, and four patients developed multifocal CNS relapse.

## DISCUSSION

High-grade gliomas (HGG) primarily affect adult patients and are associated with a uniformly fatal outcome. Malignant gliomas account for only 10% of paediatric CNS tumours and include a large variety of heterogeneous tumours such as anaplastic astrocytomas, glioblastoma multiforme, anaplastic oligoastrocytoma, gliomatosis and diffuse intrinsic brain stem gliomas [1]. Most of our knowledge regarding HGG in childhood come from single institution reports, and only two co-operative studies have been previously reported [2, 5]. Considering high-dose chemotherapy, five series have been previously reported in the English literature [6–10]. Due to the rarity of this disease in childhood, single institution pilot or phase II studies tend to report heterogeneous groups of patients, as does this report. Thus, the conclusions of these studies have to be viewed with caution. However, this series comprises the largest group of children with HGG ever reported.

There are several objectives to be considered when evaluating the benefit of high-dose chemotherapy for malignant brain tumour of childhood. To become a standard treatment, high-dose chemotherapy must prove to be superior to conventional treatment and thus to demonstrate a dose–effect relationship. Ancillary objectives are to delay or to avoid radiation therapy in young children, and to decrease long-term toxicities. The 29% objective response rate to high-dose chemotherapy confirms previous reports [6–10] and compares favourably to response rates observed with conventional dose chemotherapeutic regimens.

The nitrosoureas appear to be the most active single agents for treating malignant gliomas. Other agents have been assessed with a modest antineoplastic activity, such as teniposide, procarbazine, hydroxyurea, carboplatin and cisplatin [11]. Since BCNU shows a steep dose–response relationship in *in vitro* and animal tumour system studies, it has been proposed for dose-intensification schedules. More than 200 adult patients with high-grade glioma have been treated using high-dose BCNU followed by bone marrow rescue [12–15]. Response rates range from 18 to 60% [16]. Despite these encouraging results, the potential benefit of this procedure remains unclear. Most patients enrolled in these studies had a better performance status and were younger than unselected patients and, therefore, selection bias may account for significant differences of as much as 2- to 3-fold in survival time [17].

More recently, high-dose chemotherapy has been proposed in children. Due to the potential toxicity of BCNU, paediatric neuro-oncologists developed protocols based on non-nitrosourea regimens. Etoposide, thiotepa, busulfan, carboplatin and cyclophosphamide have been combined in two- or three-drug containing schedules.

Thiotepa, an alkylating agent, has been used in solid tumours for more than 30 years. This agent exhibits a steep dose–response curve in *in vitro* models of human CNS cell lines [18]. *In vitro* studies have demonstrated excellent penetration of thiotepa and its major active metabolite, tepa, into the CSF [19]. The less than 10% response rate at conventional dose (65 mg/m$^2$) precluded its use in brain tumours [20]. However, using doses of 600–900 mg/m$^2$ with bone marrow rescue, Ahmed and associates reported four CR and five PR in 16 adults with malignant gliomas [21].

As a single agent, etoposide does not show a dose–effect relationship in glioma. Tirelli and colleagues [22] reported three responses in 18 patients with malignant glioma treated with conventional doses (200 mg/m$^2$). Giannone and colleagues observed three partial responses in 16 patients at doses of 1800–2400 mg/m$^2$ [23].

Using thiotepa in addition to high-dose etoposide with or without BCNU, Finlay and colleagues reported four CR and two PR in 10 patients with recurrent malignant gliomas [8]. Unfortunately, these promising results were not confirmed in subsequent studies. Kalifa and colleagues [9] reported one objective effect in 8 children with malignant gliomas receiving busulfan (150 mg/m$^2$/day × 4) and thiotepa (350 mg/m$^2$/day × 3). 2 out of 9 patients had a partial response in a phase I/II study reported by Kedar and associates [7], using cyclophosphamide (750 mg/m$^2$/day × 4) and thiotepa (250–300 mg/m$^2$/day × 3). In a pilot study with cyclophosphamide (2 g/m$^2$/day × 3) and thiotepa (250–300 mg/m$^2$/day × 3), three partial and one complete response out 13 patients were observed [6].

These data suggest that aggressive chemotherapy may not improve the response rate and the survival of patients with high-grade glioma. Moreover, the acute toxicity of high-dose chemotherapy in patients with neurological impairment is of great concern. While Heideman and colleagues did not observe any instance of chemotherapy-related neurotoxicity, most of the reports describe mild to severe adverse effects including altered behaviour with or without visual hallucinations, seizures, severe headache, intracranial haemorrhage, ataxia, hemiparesis, cranial nerve deficit and herniation. In a review of neurotoxic events related to high-dose chemotherapy in children with brain tumours, Kramer and associates recorded 74 incidents in 41 patients [24]. Neurotoxicity in the early period was associated with peritumoral oedema, metabolic derangement and febrile-infectious states, whereas later events were related to metabolic derangement associated with prolonged fluid and nutritional support and tumour progression. This neurotoxicity was generally reversible. Drowsiness has been reported by Kalifa and associates in 5 out of 20 patients with brain tumour treated with high-dose chemotherapy [9]. It resolved within 5–20 days in all but one patient who subsequently died of multivisceral failure. This high incidence of neurotoxic events may be related to the regimens used [25, 26], or more likely to the glial swelling induced by tumour lysis [27].

The addition of conventional dose chemotherapy to the classical standard radiotherapy treatment remains controversial. The beneficial role of chemotherapy is based on a limited co-operative study that has recently been re-evaluated [28]. Controversies regarding the eligibility criteria and pathology have weakened the conclusions of the CCG 943 study. This highlights the crucial need for new developments and large co-operative studies in this area.

When investigating a novel therapeutic approach that deviates from conventional therapy, the additional efficacy of the new strategy must be established to outweigh its toxicity. Any novel approach remains experimental until it has demonstrated a real superiority over standard protocols. High-dose chemotherapy in malignant brain tumours is feasible but does it work? Since preliminary reports of high-dose chemotherapy in high-grade glioma in children and adult patients have been promising, one may question the absence of phase III studies. The relative success of phase III studies in malignant glioma might potentially be assessed by their comparison with the results established for a comparable group of patients registered in co-operative studies using conventional chemotherapy. While waiting for the results of such studies, and since it appears that most of the promising results obtained using high-dose chemotherapy concern a highly selected population of patients, there is no reason to adopt high-dose chemotherapy as a new treatment for malignant gliomas. Nevertheless, phase II studies using new agents or new drug combinations are needed. However, due to the difficulty in assessing some results reported after studies in single institutions, it is to be hoped that future studies will be conducted by co-operative groups or reported to national or international databases to allow faster and more extensive analysis of larger populations.


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