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Review

High-grade glioma in children under 5 years of age: A chemotherapy only approach with the BBSFOP protocol

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ABSTRACT

The aim of this study was to evaluate a chemotherapy strategy that avoids radiotherapy in first-line treatment of young children with high-grade glioma. A total of 21 children under 5 years of age received the BBSFOP protocol, comprising seven cycles of three drug pairs (carboplatin/procarbazine, cisplatin/etoposide and vincristine/cyclophosphamide) administered over a 16 month period. Radiotherapy was performed in case of recurrence/progression. Median age at diagnosis was 23 months. Histology was classified as World Health Organisation (WHO) grade III in 13 and grade IV in 8. Of the 13 children with a residual tumour, chemotherapy induced 2 partial responses (PR), 1 minor response (MR) and 1 stable disease (SD) with no recurrent disease. Five-year progression-free survival was 35% and 5-year overall survival was 59%, with a median follow-up of 5.2 years. At the last update, 12 children were alive (10 without radiotherapy). In conclusion, this study shows that an adjuvant chemotherapy first approach is safe and allows radiotherapy to be avoided in selected children.

1. Introduction

High-grade gliomas represent a heterogeneous group of tumours that accounts for 15–20% of all pediatric central nervous system tumours. The current standard treatment of these tumours is surgery, followed by external beam radiation. Historically, with surgery and irradiation, only rare patients with high-grade glioma survived beyond 2 years after diagnosis.[1] On the other hand, infants are at risk for substantial treatment-related toxicity, including impairment of neurocognitive development and endocrinological deficits. Poor outcome and late treatment effects have engendered a reluctance to treat young children with radiation therapy.[2–6]

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A multimodality treatment combining surgery, local radiotherapy and chemotherapy is the standard approach for children over 3 years of age with newly diagnosed supratentorial high-grade glioma. The challenge in 1990 was to delay or avoid radiotherapy in infants and young children. Possible options were either to delay radiotherapy until a fixed age (Paediatric Oncology Group (POG), Children's Cancer Group (CCG) and HIT studies) or to restrict the use of radiotherapy at the time of relapse or progression (BBSFOP). The drugs selected were a combination of those shown to be useful in infants and young children with malignant brain tumours: procarbazine and vincristine (as in MOPP ((mustine, vincristine (Oncovin), procarbazine, prednisolone),[7]) cyclophosphamide,[8,9] cisplatin,[10] carboplatin[11] and etoposide (because it works with cisplatin). The aim was to develop a mild chemotherapy that could be given for a long period to replace radiotherapy. The same protocol was applied to all malignant brain tumours, whatever their histology, but reports were written for a given tumour type. This papers reports the outcome of the children under 5 years of age treated with the BBSFOP protocol for high-grade glioma.

2. Patients and methods

2.1. Patient eligibility

Children with high-grade glioma were eligible for the study if the following criteria were fulfilled: (i) age under 5 years at diagnosis; (ii) histologically proven grade III or grade IV glioma; (iii) no prior exposure to chemotherapy or radiotherapy; (iv) no contraindication to chemotherapy; and (v) a Lansky score over 30.

Informed consent was obtained from the parents or guardians of each child in accordance with institutional guidelines.

2.2. Pathology review

The slides were centrally reviewed by a panel of four neuropathologists. Tumours were classified according to the World Health Organisation (WHO) classification.[12]

2.3. Surgery

All patients underwent neurosurgery with the goal of maximal surgical resection. Resection was deemed complete when the neurosurgeon and neuroradiologist confirmed the absence of residual tumour at the end of the operative procedure. Early imaging-documented extents of resection (i.e. before day 3) were defined according to the guidelines of International Society of Paediatric Oncology (SIOP).[13] Resection was considered to be subtotal when at least 90% of the tumour had been removed. All other resections were considered as partial.

2.4. Treatment regimens

Chemotherapy should start within 1 month after surgery. The regimen consisted of seven cycles of chemotherapy at 3-weekly intervals using alternating courses of:

- carboplatin 15 mg/kg (450 mg/m^2/d) in a 1-h infusion on day 1
- procarbazine 4 mg/kg/d (120 mg/m^2/d) orally on days 1–7

and

- etoposide 5 mg/kg/d (150 mg/m^2/d) in a 1-h infusion on days 22 and 23
- cisplatin 1 mg/kg/d (30 mg/m^2/d) in a 3-h infusion with mannitol plus saline on days 22, 23

and

- vincristine 0.05 mg/kg/d (1.5 mg/m^2/d) as an intravenous bolus on day 43
- cyclophosphamide 50 mg/kg/d (1500 mg/m^2) in a 1-h infusion with hydration and mesna (Uromitexan®) on day 43

More than 0.8×10^9 of granulocytes/l and more than $120{,}000 \times 10^9$ of platelets/l were mandatory haematological criteria to start a new course. For children over 3 years of age, doses were calculated in milligrams per square metre. Cumulated doses levels of 21 courses were 3150 mg/m^2 of carboplatin, 5880 mg/m^2 of procarbazine, 2100 mg/m^2 of etoposide, 420 mg/m^2 of cisplatin, 10.5 mg/m^2 of vincristine and 10.5 g/m^2 of cyclophosphamide.

All patients were fitted with a central line. No granulocyte colony-stimulating factor was administered. The planned duration of chemotherapy was 16 months. Chemotherapy was discontinued in case of disease progression or unacceptable toxicity. No irradiation was planned after the end of chemotherapy even in case of a persistent residue. Salvage therapy (including irradiation) was indicated for disease progression or relapse only.

2.5. Evaluation procedures

Disease extent at diagnosis was assessed by means of a spinal magnetic resonance imaging (MRI) study and colony-stimulating factor (CSF) cytology. The neuroradiological follow-up consisted of a cranial MRI every 3 courses during the treatment, then every 6 months. Spinal MRI and CSF cytology evaluations were performed if symptoms occurred. Audiograms were performed before every course containing cisplatin and every 2 years after the end of chemotherapy. Neurodevelopmental tests were scheduled to be informed postoperatively in neurologically stable children, then every 6 months during treatment. After treatment, a complete neuropsychological evaluation with the Brunet-Lezine or Wechsler scales adapted to the age of the child was mandatory.

Radiological postoperative residues and responses were evaluated by the individual investigators during chemotherapy and centrally reviewed retrospectively using the standard SIOP criteria.[13] The central review analysis included at least imaging studies before chemotherapy for patients with complete resection and at the end of chemotherapy for all patients. The best response at any time after the start of chemotherapy was retained for evaluation. Persistent continuous remission (PCR) was defined as no recurrent disease after complete resection. Complete response (CR) was defined as a complete disappearance of tumour after treatment. Partial response (PR) and minor response (MR) were defined as greater than 50% but lower than 90% reduction or 25–50% reduction, respectively, in the product of the two longest

perpendicular diameters of the tumour on MRI. Disease progression was documented radiologically (with or without clinical signs).

2.6. Statistical analysis

Overall survival (OS) rates were estimated using the Kaplan–Meier method,[14] from the first day of chemotherapy to death or the date of the last of the follow-up visit for patients who were still alive. Progression-free survival (PFS) rates were estimated from the first day of chemotherapy to the time of documented failure (date of the progression for patients whose disease progressed before achieving complete remission,[15] time of relapse or time of death for the others) or to the date of the last follow-up visit for those remaining in first CR.

3. Results

Patient characteristics are summarised in Table 1.

3.1. Study population

Between October 1990 and June 2002, 21 children (10 boys, 11 girls) were treated for a high-grade glioma with the BBSFOP protocol.

The median age at diagnosis was 23 months (range 1–47 months). No patient had neurofibromatosis type 1. The location of the tumour was supratentorial in 17 children and infratentorial in 4 patients. The primary tumour site was within the cerebral cortex (12 patients), midline (5 patients) and posterior fossa (4 patients). No metastatic cases were reported at diagnosis. Surgery, as assessed by the neurosurgeon, was complete in 7, subtotal in 2 and partial in 9. A biopsy only was performed in 3 patients. Residual tumour was present in 13 and absent in 8 patients on early postoperative imaging studies. In 1 case only, there was a discrepancy between a surgeon reported subtotal exeresis and no residue on MRI. Residual tumour was found after surgery of 1 case of infratentorial tumour and 12 cases of supratentorial tumour.

Pathology review was performed for all patients. In 20 cases, the initial diagnosis was confirmed: anaplastic oligodendroglioma in 3, oligodendroglioma in 4, astrocytoma in 7, glioblastoma in 5 and oligoastrocytoma in 1 case. In 1 patient, the initial diagnosis was ependymoma but was reclassified as anaplastic oligodendroglioma.

3.2. Tumour response to the BBSFOP protocol and survival

Of the 13 children with residual tumour, 2 had a PR after 1 cycle (3 courses and 2.5 months of treatment) and 1 patient had an MR after 3 cycles of chemotherapy. One patient with a postoperative residue, had SD with no recurrent disease at last update with a follow-up of 26 months. Median time to relapse/progression was 10 months (range 1–104 months) in 13 patients who had postoperative residual disease. During chemotherapy, relapse occurred in 3 out of 7 patients who had complete resection. The 5-year PFS in the whole series was 35.3% (95% confidence interval (CI) 16–52%) and the 5-year OS was 58.8% (95% CI 34–73%) with a median follow-up of 5.2 years (9 months–12.6 years) (Fig. 1).

Table 1 – Patient characteristics, treatment and outcome

Patients	Old (months)	Tumor location	Histology	Resection	Residual tumor	Response	Time to relapse (months)	Survival (months)
Age > 2 years								
1	46	Cerebral hemisphere	AO	Partial	x	PD	10	21
2	38	Cerebral hemisphere	OA	Partial	x	PD	11	86
3	39	Midline	A	Complete		PD	8	9+
4	30	Midline	A	Partial	x	MR	47	102+
5	35	Cerebral hemisphere	O	Complete		PCR		68+
6	39	Cerebral hemisphere	AO	Partial	x	PD	14	68+
7	42	Midline	GBM	Biopsy	x	PR		68+
8	36	Cerebral hemisphere	O	Partial	x	PD	6	13
9	47	Midline	O	Biopsy	x	PD	1	9
10	40	Cerebral hemisphere	GBM	Complete		PD	3	7
Age < 2 years								
11	22	Cerebral hemisphere	A	Subtotal		CR		63+
12	12	Cerebral hemisphere	A	Biopsy	x	PD	3	57+
13	2	Cerebral hemisphere	AO	Complete		PCR		22+
14	21	Cerebral hemisphere	AO	Subtotal	x	PR	104	152+
15	11	Midline	O	Partial	x	SD		26+
16	1	Cerebral hemisphere	GBM	Partial	x	PD	1	10
17	23	Posterior fossa	GBM	Partial	x	PD	1	10
18	14	Posterior fossa	GBM	Complete		PCR		83+
19	12	Posterior fossa	A	Complete		PD	7	12
20	4	Cerebral hemisphere	A	Partial	x	PD	5	11
21	12	Posterior fossa	A	Complete		PCR		30+

PD, progressive disease; CR, complete remission; SD, stable disease; PR, partial response; MR, minor response; PCR, persistent continuous remission; AO, anaplastic oligodendroglioma; O, oligodendroglioma; GBM, glioblastoma; OA, oligoastrocytoma; A, astrocytoma.

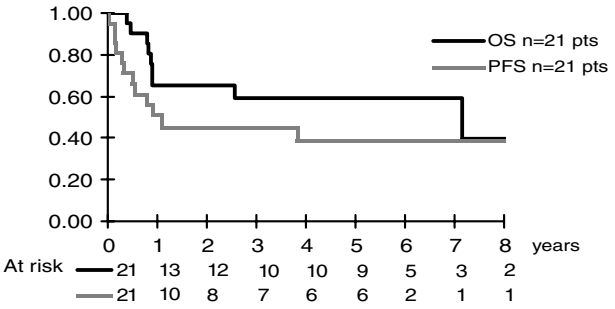

Fig. 1 – Overall survival (OS) and progression-free survival (PFS).

Table 2 shows the salvage treatment of the first relapse or progressive disease. Progression or relapse was diagnosed in 14 patients, 2–103 months after the initiation of chemotherapy (median 6 months). In 12/14 children, the disease progressed or relapsed during chemotherapy, i.e. during treatment. The first event was a local failure in 11 patients, local and distant in 2, and distant in 1. The distant sites were brain metastases in 2 cases and leptomeningeal spread in 1 case. Of these 14 relapsing patients, 3 are alive and disease-free at 42, 48 and 52 months after the relapse. After a second relapse, none of the patient achieved a third complete remission (CR3).

At the last update, 9 patients had died from progressive disease, 5–83 months after the initiation of chemotherapy (median 10 months). Among the 12 survivors, 5 were in CR1, 2 in CR2 with radiotherapy, 1 in CR2 without radiotherapy, 3 had SD and 1 had progressive disease and had not been treated with radiotherapy.

No patient received radiotherapy as part of their first-line treatment. Six patients were treated with local irradiation as part of salvage treatment of the first relapse. At the last follow-up visit, 10 patients were still alive without radiotherapy with a median follow-up of 5 years. Of these 10 patients, 6 were alive without recourse to radiotherapy more than 5 years after initiating chemotherapy.

3.3. *Toxicity*

Chemotherapy was well tolerated. The median number of courses administered in the 21 patients was 15. Treatment was never discontinued because of toxicity. In particular, no acute ototoxicity was encountered and cisplatin courses were administered to all patients as planned in the protocol. The BBSFOP chemotherapy regimen was stopped prematurely in 12 patients, always because of progression or relapse. Among the 288 courses administered, 25 resulted in complications (8.6%). No toxic death occurred. Grade IV neutropaenia occurred in 15 courses (5.2%). Five documented, easily treatable infections (*Staphylococcus epidermidis* septicaemia in 2, varicelle in 2 and folliculitis in 1) were observable in 4 patients. Only 5 children had blood or platelet transfusions. No allergy to carboplatin was observed. To date, no second tumours have occurred in this cohort.

At the last follow-up visit the neurological status was considered normal in 8 of 11 evaluated children. One child had monoparesis. One patient had a visual deficit and 1 had oculomotor problems. No patient had significant hearing loss (i.e. hypoacousia). Neurodevelopment, as reported by the clinician, was normal in 9 children; data were missing for 3 patients. Among the 12 children survivors, neuropsychological evaluation was performed in 7 patients at a median of 24 months (range 0–54 months) after the end of treatment. The mean full scale intellectual quotient was 81.6 (range 55–104).

3.4. *Risk factor analysis*

Fig. 2 shows the outcome of the patients after stratified the population according to the risk factors identified *a priori*:

Table 2 – Salvage treatment of progressive disease or at first relapse

Patients	Response	Time to relapse (months)	Relapse	Surgery	Radiotherapy (Gy)	First-line chemotherapy	Survival (months)
Age > 2 years							
1	PD-L	10			55	VP/CBO	21
2	PD-L	11		Complete resection	52		86
3	PD-L	8					9+
4	SD	47	PD-L + D			VCR/CBO	102+
6	PD-L + D	14		Incomplete resection	40	VPCBO/VCRCPM	68+
8	PD-L	6		Incomplete resection		PCV, Temozolomide	13
9	PD-L	1				PCV, oral VP	9
10	PD-L	3			54		7
Age < 2 years							
12	PD-L	3		Complete resection		VP/CBO	57+
14	PR	104	PD-L	Complete resection	55		152+
16	PD-D	1				Temozolomide	10
17	PD-L	1				Temozolomide	10
19	PD-L	7		Complete resection	45		12
20	PD-L	5					11

PD-L, progressive disease local; PD-L + D, progressive disease local and distant sites; PD-D, progressive disease at distant sites; VP/CBO, etoposide/carboplatin; VCR/CBO, vincristine/carboplatin; VCRCPM, vincristine/cyclophosphamide; oral VP, oral etoposide.

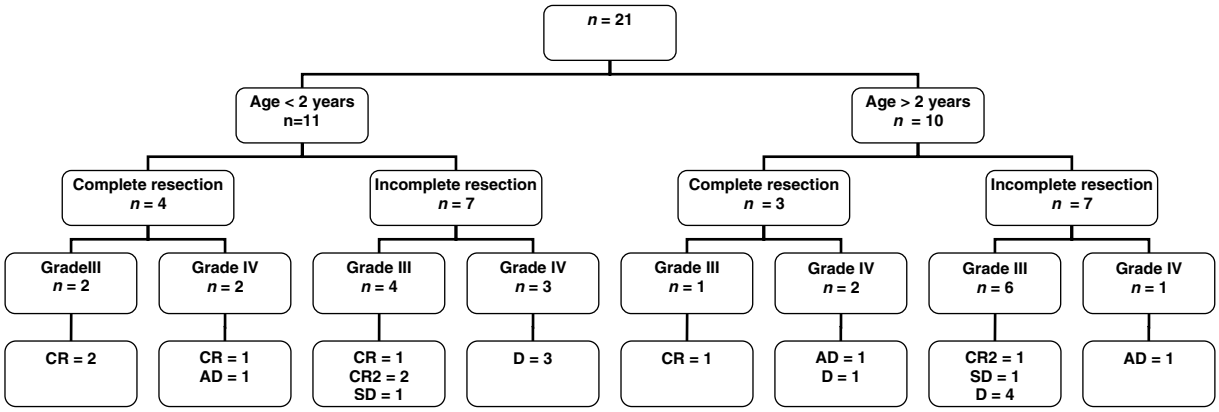

Fig. 2 – Outcome in relation to age, tumor histology and extent of resection. CR, complete remission; SD, stable disease; D, death; AD, alive with disease.

age below 2 years, quality of resection and histological grading. Six out of 11 children under 2 years of age were alive in CR compared with 2 out of the 10 patients older than 24 months (P = not significant). Seven out of 13 children with grade III tumours were alive in CR compared with only 1 out of 8 children with grade IV tumours (P = not significant). Five out of the 7 children who had complete surgical resection were alive, while 7 out of the 14 incomplete resection were alive (P = not significant).

4. Discussion

Information about outcome of children younger than 3 years with supratentorial high-grade gliomas is scanty because the number of affected patients is very small. The survival of infants and very young children with brain tumours is significantly worse than that of older children, both overall and within specific tumours types. Not only are survivals poor, but infants tend to suffer the brunt of treatment-induced neurotoxicity. We investigated the treatment of high-grade gliomas without irradiation to avoid the deleterious neuropsychological affects that are particularly pronounced in infants and young children. The finding of paramount importance in this study is that a significant proportion of children with high-grade glioma can be cured without irradiation. Indeed, among the 21 patients, 10 children were alive without receiving radiotherapy (8 in CR). In our study, chemotherapy induced two partial responses, one minor response and one prolonged stabilisation. While no phase II trials have been conducted specifically in this age group, several studies have been performed using different multidrug regimens. In most of these studies, evidence for the activity of each agent is poor or even non-existent.[16] However, this approach could be sufficient for minimal disease. In selected children without residual disease, chemotherapy alone provided excellent control of disease. There are only two published studies (Baby POG I, CCG 945), in which postoperative chemotherapy was given in children under 5 years of age with high-grade glioma.[17,18] Isolated cases can be found in some of the infant study reports mixing different histology subtypes but their number is too small to draw even prudent conclusions. In the Baby POG I study, 18 children under 36 months of age with diagnosed malignant brain tumours were treated postoperatively with two 28-d cycles of cyclophosphamide plus vincristine, followed by one 28-d cycle of cisplatin plus etoposide. This sequence was repeated until the disease progressed, in order to delay radiotherapy until the age of 3 years. Of the 10 children who had residual tumour following surgery, 6 had partial responses to two cycles of cyclophosphamide and vincristine.[18] Four children were not irradiated after 24 months of chemotherapy and, none have developed recurrent disease.[19] By contrast, the CCG found less encouraging responses to the 8-in-1 treatment in their 32 children under the age of 2 years with malignant gliomas. Of the 21 patients with measurable postoperative tumour, the objective response to two cycles of chemotherapy was 24%. In this study, 13 of 32 children were still alive without irradiation.[17]

Although the numbers of children studied were limited, we had encouraging results in children with malignant gliomas. The 2-year PFS and OS rate of 45.4% (95% CI 16–52%) and 65% (95% CI 34–73%), respectively, are comparable to those reported for high-grade glioma in the Baby POG I study, in which irradiation was delivered at the end of chemotherapy.

Age at diagnosis, histological diagnosis and extent of surgical resection were investigated as potential prognostic factors (Table 3).

It seems that children under 2 years of age have a better prognosis in our study. However, in other studies, age was not found to have an influence on survival.[18] Larger studies or meta-analysis might provide a definite answer to this question.

No statistical difference in survival rates was demonstrated between the two histological features: grade III and grade IV. In the literature, however, there was a statistically significant difference in outcome between patients with reviewed diagnoses of grade III tumours and grade IV tumours.[1,20,21] In the CCG 945 study, the 3-year PFS rates for the anaplastic astrocytomas group was 44% (standard error (SE) 11%), while all infants with a diagnosis of glioblastoma multiforme have failed within 3 years.[17] In the Baby POG I study, pathology had no influence on survival.[19] However, one must consider that these studies were published prior

Table 3 – Review of prognostic factors: age at diagnosis, histological diagnosis and extent of surgical resection

	Age (months)		Histological diagnosis			Surgical resection	
	<24	>24	AA	GBM	Others	Complete	Incomplete
CCG 945 (17) $n = 32$	32	0	20	8	4	23	9
				$P < 0.001$		P = ns	
Baby POG I(18) $n = 18$	16	2				6	11
	P = ns			No details		P = ns	

to the final central pathological review. The CCG 945 study demonstrated the importance of central pathological review in studies of children with high-grade glioma. The proportion of oligodendroglioma (42.8%) seems to be higher in our series. However, comparison with other series is difficult because these tumours are sometimes excluded from studies on malignant gliomas and most often are reported in a subgroup named 'grade III glioma' or 'others malignant gliomas'. Three oligodendrogliomas out of 41 patients (7.3%) treated for a supratentorial malignant glioma were reported in a series of the St Jude Children's Research Hospital.[22] Moreover, histological diagnosis and grading of oligodendroglial tumours remain controversial and the problem of inter-observer reproducibility persists.[23]

Despite the absence of a significant difference in survival according to extent of surgery, patients with complete resection (i.e. absence of post-operative radiological residue) were less likely to fail this chemotherapy. The positive impact of complete surgery on OS has been reported extensively in the literature in adults and in children, but also in the Baby POG I study the degree of surgical resection had no influence on survival, probably because, as in our study, the number of patients was too small.[18]

The preliminary data on the cognitive development of patients in this study suggests that the strategy may impact favourably on the intellectual outcome of these young children compared with those treated with local irradiation alone in earlier studies.[2]

In conclusion, our overall results did not appear to be different from those obtained in young children treated with adjuvant chemotherapy and standard radiation. Delaying the use of radiotherapy at the time of relapse did not preclude the overall survival of the entire cohort. In selected children (47.6% of the children included in this study), chemotherapy alone provided excellent control of malignant tumours and enabled radiotherapy to be avoided. These encouraging results with prolonged and low dose-intensity chemotherapy should warrant further assessment in large co-operative groups. The favourable outcome of these young patients, despite the avoidance of radiotherapy in many cases, raises some questions about possible different behaviour of these tumours in infants. Due to the rarity of these tumours, there is a need for international co-operation to address the numerous questions remaining for the management of these young children.

Conflict of interest statement

None declared.

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