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Carboplatin before and during radiation therapy for the treatment of malignant brain stem tumours: a study by the Société Française d'Oncologie Pédiatrique

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Abstract

Childhood malignant brain stem tumours have a very poor prognosis with a median survival of 9 months despite radiotherapy. No chemotherapy has improved survival. However, carboplatin has been reported to have activity in glial tumours as well as antitumour synergy with radiation. Our aims were to test the response rate of these tumours to carboplatin alone and to evaluate the efficacy on survival of carboplatin alone followed by concurrent carboplatin and radiotherapy. Patients younger than 16 years with typical clinical and radiological presentation of infiltrating brain stem tumour, as well as histologically-documented cases in the atypical forms, were eligible. Two courses of carboplatin (1050 mg/m^2 over 3 days) were administered initially. This treatment was followed by a chemoradiotherapy phase including five weekly carboplatin courses (200 mg/m^2) and conventional radiotherapy. 38 eligible patients were included. No tumour response was observed after the initial phase. This schedule of first-line carboplatin followed by concurrent carboplatin and radiotherapy did not improve survival. © 2002 Published by Elsevier Science Ltd.

Keywords: Brain stem tumour; Children; Carboplatin; Radiotherapy

1. Introduction

Childhood malignant brain stem tumours still carry a very poor prognosis with a median survival of 9 months after diagnosis, despite transitory improvements of neurological signs often observed after the use of conventional radiation therapy [1,2]. Trials of hyperfractionated radiotherapy have recently been used without showing any improvement of survival [3,4].

The use of chemotherapy after or during radiation has never been shown to be able to improve survival [2,5–8], even with the use of high-dose chemotherapy with haematopoietic stem cell rescue [9]. The use of neoadjuvant chemotherapy with cisplatin and cyclophosphamide before hyperfractionated radiotherapy has also been reported [10]: although minor responses

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have been observed in rare instances, as in other limited studies with neoadjuvant chemotherapy [11], concurrent chemo- and radiotherapy [12], or intra-arterial chemotherapy [13], no improvement of survival was achieved. However, the use of neoadjuvant chemotherapy and evaluation of tumour response in brain stem tumours still appears to constitute a logical step for the screening of active cytotoxic drugs which might be useful for the treatment of this disease.

Carboplatin is an active drug in childhood brain tumours [14] and its toxicity is well known [15]. The use of carboplatin seems to be more rational than cisplatin because of better brain penetration [15] and evidence of decreased ototoxicity by comparison to cisplatin [16]. The activity of carboplatin in malignant glioma has been reported in adults [17] and in children [14,18]. The known synergy between platinum compounds and irradiation [19] prompted us to use carboplatin during radiotherapy to try to potentiate the antitumour effect of irradiation.

This multicentric study was designed to test the efficacy of up-front carboplatin alone in malignant brain stem tumours, and to evaluate the efficacy of the sequence carboplatin alone followed by carboplatin plus radiotherapy, in terms of survival.

2. Patients and methods

2.1. Inclusion criteria

Patients less than 16 years old were eligible. The diagnosis of malignant brain stem tumour was based on neuroradiological criteria of infiltrating brain stem tumour on magnetic resonance imaging (MRI) scan [20], a biopsy was not mandatory except in the case of uncertain diagnosis or atypical presentation. No treatment other than corticosteroids and, if necessary a cerebrospinal fluid (CSF) shunt, was allowed before initiation of carboplatin. Haematological, renal, hepatic and audiometric assessments had to show a maximum of Who Health Organization (WHO) grade 2 toxicity prior to carboplatin. Ethical approval of the protocol has been obtained according to the French law. The parents' or guardians' informed consent was mandatory.

2.2. Treatment

Two courses of carboplatin were administered before radiotherapy. Each course consisted of 350 mg/m^2/day of carboplatin from day 1 to day 3 diluted in isotonic dextrose as a 1-h infusion. The interval between the two courses was as brief as possible after achieving 80×10^9 cells/l platelets and 0.8×10^9 cells/l neutrophils during the haematological recovery phase. Platelet count was to be maintained above 50×10^9 cells/l throughout treatment to avoid intratumoral bleeding. Detailed neurological and general clinical examination was performed at baseline and after one and two courses; the presence of steroid dependency was noted. In the case of neurological deterioration after one course, neuroradiological assessment was requested to avoid a second course when the disease was progressing. Comparative MRI with three-dimensional measurements of tumour size and description of tumour appearance and Gadolinium uptake was planned after the initial phase of carboplatin alone.

This chemotherapy phase was followed by a concurrent chemoradiotherapy phase which included a weekly infusion of carboplatin (200 mg/m^2 as a 1-h infusion once a week for 5 consecutive weeks) and conventional radiotherapy. This phase was planned to start at the latest 4 weeks after the second course of high-dose carboplatin, after achieving 80×10^9 cells/l platelets/m^3 and 0.5×10^9 cells/l neutrophils during the haematological recovery phase. The planned radiotherapy total dose was 54 Gy delivered over 6 weeks with a daily dose of 1.8 Gy per fraction in the procubitus or dorsal decubitus position, with a recommended contention system. Two parallel lateral opposites fields and the use of photon energy greater than 10 MeV were recommended. Target tumour volume was defined on MRI after two courses of carboplatin with a 2-cm safety margin.

2.3. Quality controls and statistical analysis

The primary endpoint was 9-month survival. Secondary endpoints were clinical neurological outcome, steroid dependency and tumour response evaluated on MRI. Central review for all MRI scans at diagnosis, most MRI after two courses of carboplatin—including all MRI scans which were coded as a partial or objective tumour response by local investigators—was also performed by a panel of four radiologists. A panel of four neuro-pathologists has centrally reviewed the histology of the biopsy specimen.

The statistical analysis of this phase II study was based on a triangular test [21]. Alpha risk (error of the first kind) was 10% and the beta risk was 5%. A 9-month survival rate of less than 50 or greater than 70% was considered to be the upper limit for ineffective treatment, or the lower limit for effective treatment, respectively. The 9-month survival rate was analysed every 5 patients followed for at least 9 months. When performing an interim analysis, cumulative results were reported on the triangular figure. The trial was to be stopped either if the upper boundary was crossed (rejection of H0, benefit from the proposed strategy, that is a 9-month survival rate superior to 50%), or if the lower boundary was crossed (non rejection of H0, no evidence of benefit). As long as no boundary were crossed, additional patients were to be included and/or followed.

3. Results

3.1. Patient population

Between November 1991 and January 1994, 42 patients from 12 centres were registered in the study. 4 patients were excluded from the analysis because of inappropriate diagnosis (1 cerebellar peduncular glioma, 1 surgically removed exophytic brain stem tumour, 1 case of rhombencephalitis), or lack of data (1 case). 38 patients were therefore included in the analysis: 10 males and 28 females, ranging in age from 3 to 15 years (median 6 years). Location of the tumour is reported in 35 patients. All the 35 tumours involved the pons: 13 were also developed within the midbrain and 14 within the medulla and the midbrain.

14 patients underwent biopsy, including 3 patients who underwent partial surgery. Central review of the biopsy specimens was performed in 11 cases and showed high-grade astrocytoma (7), and low-grade astrocytoma (4). All 38 patients had the required neuroradiological criteria, including 4 patients with so called 'low-grade astrocytoma' at biopsy.

3.2. Initial chemotherapy phase

36 of the 38 patients were evaluable: 1 patient did not receive the initial chemotherapy phase and MRI data were missing for the other patient. One patient received only one course because of early progression. The clinical outcome after the two courses of chemotherapy was described by the investigators as deteriorated in 13 patients, improved in 6 patients, and stable in 17 patients. The need for corticosteroids before and after the initial phase of carboplatin therapy was known for 33 patients. 6 of them did not require corticosteroids during this phase; 9 patients needed an increased dose of corticosteroids, 5 required a stable dose and the dosage could be decreased in 13 patients. The radiological response to the initial phase of carboplatin therapy was centrally reviewed in 21 patients, including the only 4 patients for whom local investigators suggested a radiological response. In 2 patients, analysis of tumour response was not evaluable. No partial response was observed, 2 radiological improvements were reported, but 1 of these cases developed distant tumour nodules; progressive disease appeared in 11 patients and stable disease in 6 patients.

3.2.1. Toxicity of the initial chemotherapy phase

No toxic death was observed. One patient did not receive the planned chemotherapy because of prolonged postoperative hospitalisation in an intensive care unit. Short-term toxicity data are known for 71 courses (including the 37 first courses); the second course was omitted once because of progressive disease. Grade IV neutropenia was observed in 25 courses in 17 patients, with a duration of 3–17 days (median: 7 days). Leucopenia less than 1×10^9 cells/l was observed in five courses for 4 patients, with a duration of 1–11 days (median: 5 days). Neutropenia less than 0.5×10^9 cells/l was observed in 25 courses for 17 patients, with a duration of 3–17 days (median: 7 days). Platelet counts less than 50×10^9 cells/l were observed in 39 courses for 26 patients with a duration of 1–12 days (median: 4 days). Red blood cell transfusions were necessary in 16 courses in 16 patients and platelet transfusions were necessary in 44 courses in 27 patients. Fever above 38.5 °C was observed after 12 courses with a duration of 1–16 days (median: 3 days); in 10 of these courses, intravenous (i.v.) antibiotics were necessary during 3–58 days (median: 7 days).

3.3. Chemoradiotherapy phase

In 2 patients, radiotherapy was not performed because of tumour progression. The time interval between the initiation of treatment and the start of radiotherapy was 26–68 days (median: 58 days). The doses delivered to the brain stem varied from 45 to 57 Gy (median: 54 Gy). Radiation therapy had to be interrupted in 3 cases for medical reasons, and in 2 cases for technical reasons. All patients survived the radiotherapy period except 1 patient who deteriorated clinically and died after the third fraction of radiotherapy. 27 patients received the planned five courses of weekly carboplatin. Two patients received six courses. Carboplatin was not given in 3 patients because of altered clinical status. One patient received only one course before early death during radiation therapy. 2 patients did not receive the last two courses because of medical complications (pneumothorax, meningitis). One patient received four of the five courses. Chemotherapy was well tolerated: 26 patients experienced no toxicity. 3 patients had grade IV neutropenia for 1, 11 and 12 days; 4 patients had platelet counts below 50×10^9 cells/l for 1, 5, 6 and 7 days; and 1 patient had leucopenia below 1×10^9 cells/l for 14 days. 4 patients received platelet transfusions and 3 red blood cell transfusions.

3.4. Survival

The 9-month survival rate was $65.8\pm15\%$. Median duration of survival of these 38 patients was 11 months (65.8%; 95% CI: 50.7–80.9) (Fig. 1). Although none of the limits defined by the initial statistical design had been reached, we decided to close the study due to the lack of improvement in survival. When the study was stopped, 30 patients had a follow-up of 9 months or more: among these 30 patients, 22 had evolutive disease and, among them, 13 were dead at 9 months and 15 at 10 months. The survival of the 3 patients that under-

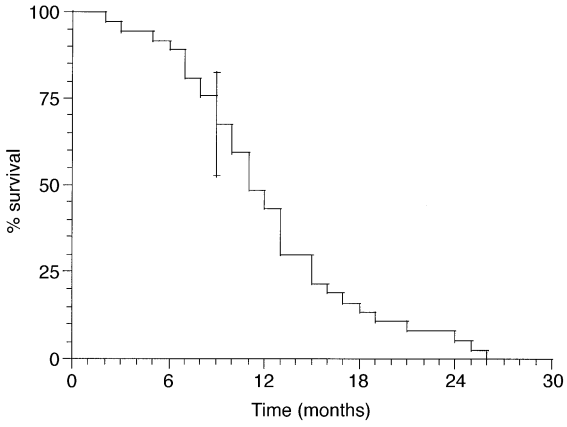

Fig. 1. Survival curve of 38 eligible patients. The survival rate at 9 months is 65.8% and at 11 months 47.4%. The study was stopped when the 9 months follow-up was reached in the first 30 patients, showing either death or progressive disease in more than 50% of the patients.

went initial partial resection was 4, 9 and 15 months. None of the 38 patients survived after 26 months.

4. Discussion

The median survival in this series was not worsened by giving upfront chemotherapy, in comparison to previous studies but, as for other cytotoxic drugs [22], no significant benefit of carboplatin was observed in terms of survival. Because of the difficulties in evaluating tumour modification during therapy [23], taking into account the infiltrating nature of the disease, MRI changes due to corticosteroids and the poor prognosis, further clinical studies concerning the treatment of malignant brain stem tumours should still use the survival rate as the main endpoint rather than the evaluation of tumour response. We decided to close the study after the inclusion of 38 eligible patients and after 9 months of follow-up of the first 30 patients, although 17 patients were still alive (9-month survival rate of these first 30 patients: 56.7%). Indeed, among these 17 patients, only 8 did not show evidence of clinical progression at 9 months. Although the observed 9-months survival of the 38 patients is 65.8%, near the chosen upper limit of 70%, the median survival time of the whole group is only 11 months and all the patients were dead within 26 months after diagnosis. To continue the inclusion of patients seemed to us unethical. Although the toxicity of this drug regimen was tolerable, the quality of life of children with brain stem tumour, already impaired by neurological alteration, has probably been further compromised by the use of conventional chemotherapy because of digestive and haematological adverse effects. Except in the case of a totally new mechanism of action, the use of cytotoxic drugs or combinations of drugs is therefore probably no longer justified in a neoadjuvant situation.

However, attempts to potentiate the effect of radiotherapy may still constitute another way to improve the outcome. The only two treatment modalities which have been clearly shown to have a short-term clinical effect, are radiation therapy and corticosteroids. Corticosteroids might have only an anti-oedematous effect unlike radiotherapy which probably has a real antitumour effect. However, radiotherapy alone is not curative and the use of higher doses and hyperfractionation or acceleration does not improve survival [24,25]. Attempts to potentiate radiation therapy have already been conducted in brain stem glioma, using interferon [26], tamoxifen [27] or cytotoxic drugs [28]: no benefit of any of these strategies was observed on survival.

Potentialisation of the effects of radiation therapy by platinum compounds has a biological and preclinical basis [19,29]. Encouraging results of this combination have also been reported in recent clinical trials [30]. Furthermore, the rationale for using chemotherapy in brain stem glioma might be not only to potentiate the effect of radiation therapy, but also to decrease the risk of leptomeningeal disease [31]. However, our study using weekly infusions of carboplatin associated with conventional radiation therapy did not appear to improve survival of patients with brain stem glioma. Although more intensive than the 3-weekly schedule reported in concurrent chemotherapy and radiotherapy protocols for the treatment of patients with glioblastoma multiforme [32], this weekly schedule of carboplatin might not have been the most potent radiosensitiser, as observed with other drugs [33]. A twice-weekly schedule of carboplatin associated with hyperfractionated radiotherapy was recently reported for brain stem glioma, but also failed to demonstrate any significant improvement of survival [34]. Daily use of radiosensitiser before delivering the daily fraction of radiation dose might be more effective [30].

We conclude that the schedule of first-line carboplatin followed by concurrent carboplatin and radiotherapy is not effective in the treatment of malignant brain stem tumours. Like other malignant glial tumours of childhood [35], new drugs with new mechanisms of action, including radiosensitisation, are needed in this high-risk disease.

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