Pre-irradiation Chemotherapy for Newly Diagnosed High Grade Astrocytoma

N. TUBIANA MATHIEU1, D. GENET1, F. LABROUSSE2, P. BOUILLET3, S. LAVAU DENES1, J. MARTIN1, J.L. LABOUREY1, L. VENAT3, P. CLAVERE3 and J.J. MOREAU4

1Department of Medical Oncology and Radiotherapy, 2Service d’Anatomopathologie, 3Service de Radiologie and 4Service de Neurochirurgie, CHU Dupuytren, 2 avenue Martin Luther King, 87042 Limoges Cedex, France

Abstract. The purpose of this work was to determine the response rate and toxicity of a combination of Carmustine and Cisplatin administered before radiation in patients with newly diagnosed high grade astrocytoma. A good response rate has been published with this association in primary cerebral high grade tumor. This protocol was administered in a homogeneous population of 37 adult patients with measurable tumor on magnetic resonance imaging (MRI) or CT scan. After biopsy or subtotal resection, the patients received BCNU 40 mg/m2/d and CODP 40 mg/m2/d, for 3 days every 28 days for 3 cycles. Evaluation was performed before each cycle. Radiation therapy began 4 weeks after completing the chemotherapy or immediately if there was evidence of tumor progression on chemotherapy. Seven out of 37 (19%) demonstrated tumor regression with a median duration to progression of 11 months. Median survival was 6 months. Myelosupression was the predominant but manageable toxicity. This work indicated that the first chemotherapy protocol gave poor results in a homogeneous group of patients, with bad prognosis.

The initial therapeutic approach consists of surgical resection. It is rarely curative due to infiltration of tumor cells into the surrounding brain parenchyma and migration inside the brain. Resection represents a prognostic factor since there is a good correlation between patient survival and complete resection (3). However, resection is frequently impossible because of the volume or location of the tumor at a vital brain site.

Post-operative radiotherapy produces only a minor prolongation in survival with median survival, increasing from 4.5 - 6 months in the case of surgery alone to 9-10 months for a combination of surgery and post-operative radiotherapy (4).

Chemotherapy has a limited impact on the survival, despite meta analyses of randomized cases which suggested a survival benefit of 5% to 10% at two years by adjuvant chemotherapy for high grade astrocytoma (5,6). Median survival increased from 9.4 to 12 months. The most commonly used chemotherapy consisted of nitrosoureas such as Carmustine (7). The timing of chemotherapy and radiotherapy is the subject of much debate. It is believed that the blood-brain barrier is more permeable to the penetration of cytotoxic drugs before radiotherapy rather than after, and that tumors are intrinsically less resistant prior to radiotherapy. However, some patients have chemoresistant tumors and therefore require early radiotherapy.

We report the results of a pre-irradiation chemotherapy protocol, described first by Grossman et al. (8), used in 37 adults with a glioblastoma for whom complete resection was impossible. Planning of the protocol was based on Grossman’s published results. Chemotherapy relied on a combination of 2 effective drugs: BCNU and Cisplatin. BCNU administered as single-drug therapy for post-radiotherapy recurrent or progressive glioblastomas yielded a 29% response rate in glioblastomas and 64% in anaplastic astrocytomas, while the corresponding rates achieved with Cisplatin were, respectively, 73% and 83% (9).
As in the Grossman study (8), radiotherapy was performed after chemotherapy in our protocol.

Materials and Methods

Patients. The patients were adults > 18 years with newly diagnosed glioblastoma who had never received antineoplastic therapy for their brain tumor and, because of its volume of location, the brain tumor had not been totally resected. All patients had a measurable tumor and all had normal hematological parameters. Their WHO performance status was between 0 and 2. All biopsy specimens were reviewed by the same neuropathologist and analyzed in accordance with the WHO classification (10).

Treatment. The neurosurgical procedure consisted of either stereotactic biopsy or debulking surgery.

Three cycles of BCNU (40 mg/m²/d) and Cisplatin (CDDP) (40 mg/m²/d) on D1, D2 and D3 were programmed. BCNU and CDDP were each infused over 4 hours.

The interval between 2 cycles was 4 weeks if hematological parameters complied with the following criteria: WBC count > 2.5 x 10⁹/l and platelet count > 80 x 10⁹/l. Cycles were delayed until parameters complied with the following criteria: WBC count > 2.5 x 10⁹/l and platelet count > 80 x 10⁹/l. Cycles were delayed until hematological abnormalities in a patient not receiving glucocorticoids and whose neurological status was stable or improving. Progressive disease (PD) was defined as a greater than 25% increase in tumor volume on CT or MRI scan, or as a deterioration in neurological abnormalities in a patient on constant or increasing doses of glucocorticoids. Stable disease (SD) included patients whose clinical status and scan tumor volume did not satisfy CR, PR, or PD criteria. The toxicity of chemotherapy was evaluated 3 to 4 weeks after each cycle.

Survival was measured from the date of diagnosis. Overall survival was estimated using the Kaplan Meier method.

Results

Patient characteristics. Between March 1996 and July 2000, 37 patients were enrolled in this protocol (24 men and 13 women). Patient characteristics are described in Table I. Median age was 56 years (range 30 to 73 years).

Thirty-four tumors were classified as grade IV with atypical cells in 100% of the tumors, mitosis in 94%, necrosis in 97% and proliferation of the capillary endothelium in 85% of cases. Three tumors were classified as grade III since both necrosis and endothelial proliferation were absent.

Twenty-one patients only underwent a biopsy while 16 underwent partial debulking. Antiepileptic drugs and corticosteroids were administered to all patients. All patients had a measurable tumor and were assessed in terms of treatment toxicity, tumor response and survival.

Treatment. Eighteen patients (48%) completed all 3 scheduled chemotherapy cycles. Ten patients received a single cycle and 9 received 2 cycles. Of these 19 patients, 18 discontinued treatment due to progression of the disease and 1 died as a result of an intercurrent disease. No complete response was obtained. As shown in Table III, partial response (PR) was achieved in 7 patients. Four PRs were obtained after one cycle, but one patient progressed after cycle C2, while the other 3 had a better response after cycle C3. Two PRs were obtained after the second cycle and one after the third cycle. The disease was stable in 20 patients. Among patients with a partial response, the median time to progression was 11 months (1-21).

Median survival was 6 months (1-51) for all patients and 12 months (6-51) among responders (Figure 1). No response was obtained after radiotherapy among patients whose disease progressed during chemotherapy.
Feasibility. A total of 82 cycles was administered. The mean interval between 2 cycles was 37 days (32 - 44 days between C1 and C2 and 24 - 45 days between C2 and C3). Eighty-one% of patients received radiotherapy, the mean dose being 56.3 Gy. The median interval between radiotherapy and surgery was 3.5 months (range 2-6 m).

Toxicity. As shown in Table II, toxicity was mainly hematological. Grade 3 or 4 neutropenia was noted in 13 patients, including one febrile neutropenia; grade 3 or 4 thrombocytopenia occurred in 12 patients; grade 3 or 4 anemia was observed in 7 patients. Other toxic effects included: grade 2 renal damage in 2 patients which imposed the discontinuation of CDDP, one case of ketotic coma, one of ischemic stroke, one of obesity exceeding 10 kg and one of pulmonary embolism. Grade 2 - 3 nausea and vomiting occurred in 10 patients.
Discussion

The results of this study do not agree with those published by Grossman et al. (8) who used the combination of CDDP and BCNU to treat high grade brain tumors. In 52 patients with high grade astrocytomas, those authors obtained a 42% partial response rate and 53% of the patients remained stable. The partial response rate was 19% in our study. According to the initial study, the survival rate at 1 year was 62% with median survival of 13 months, whereas it was only 6 months overall in our study. The only minor difference in the 2 protocols concerned the CDDP infusion period which was 12 hours in the Grossman study compared with 4 hours in ours. There was no difference in the administration of BCNU.

The Grossman’s protocol was used in a multicenter study reported in 2000 (13) and produced more modest results than those initially obtained since there was only a CR and 4 partial responses in 47 patients.

These discrepancies underline the heterogeneous nature of glioblastomas. The low response and survival rates noted in our study might be due to the highly unfavorable prognostic characteristics of our patients. In many trials reported in the literature, patients either underwent complete resection or a biopsy and hence there was a selection process. The patients in our study were heterogeneous. All patients were over 45 years of age. Tumor persisted after surgery, and the extent of residual postoperative tumor volume is known to be a very important factor affecting median survival. Most of the tumors were grade IV. The only patient with anaplastic oligodendroglialoma had a PR and long survival time. Irrespective of the type of anticancer treatment used, prolonged survival in patients can only be predicted on the basis of prognostic factors, such as age, performance status, complete tumor resection and anaplastic astrocytoma classification (14).

The optimum timing for radiotherapy, whether before or after chemotherapy, is unclear. In the study of Grossman et al. (8), radiotherapy was performed after chemotherapy, as in protocols for pediatric brain tumors, because chemoresistance might be due to radiotherapy-induced vascular lesions or a high percentage of quiescent tumor cells during the immediate post-radiotherapy period.

However, some authors have reported disease progression in 30% of patients during pre-irradiation chemotherapy. Most authors assert that radiotherapy followed by adjuvant chemotherapy such as a nitrosourea can be regarded as standard therapy for such patients (5, 15). However, it is also possible to use a concomitant combination of two treatment strategies. The ROTG studies obtained a median survival of 9.7 months by combining paclitaxel and radiotherapy (16), and 11 months by using a combination of BCNU and radiotherapy (17).

In a randomized trial (18) carried out by Grossman’s team in 223 patients, continuous intravenous infusion of a combination of CDDP and BCNU was not found to improve survival compared with single-drug therapy with BCNU combined with radiotherapy, with a median survival of 10.7 months and 11.2 months, respectively.

It is not yet known what chemotherapy regimen would achieve the best results. Chemotherapy for brain tumors is not clearly defined, except in the case of oligodendrogliomas and oligoastrocytomas. Gliomas exhibiting oligodendroglial differentiation are chemosensitive. Caincross et al. reported a durable response rate of 75% in 33 oligodendrogial tumors treated with PCV (19).

The results are far less encouraging for grade III or IV glioblastomas, if PCV is used (20) with 45% response rate and stable disease and 15 weeks of median time to progression in recurrent gliomas. Equivalent results were obtained with cyclophosphamide-vincristine (21), carboplatin-etoposide (22) and cisplatin-etoposide (23). Their response rates were respectively 60%, 50% and 39%, and median time to progression, respectively, 15 weeks, 43 weeks and 11 weeks in gliomas after prior radiotherapy.

Meta-analyses that have compared chemotherapy followed by radiotherapy with radiotherapy alone have only found a small increase in survival: 2% in the Fine study in 1993 (5) and 6% in the most recently published meta-analysis (6). However, since the tumors concerned were not homogeneous, no meaningful conclusion can be drawn regarding the place of chemotherapy in overall treatment.

Another question could be raised with respect to the response criteria used for this type of tumor and the assessment of clinical status. Given that there is considerable edema around the tumor and that lesions are often necrotic, it is difficult to measure tumor volume.

This report indicates that it is feasible to administer a first chemotherapy regimen to patients with newly diagnosed glioblastoma but clearly new therapeutic approaches based on antiangiogenic factors, immunotherapy, or new chemotherapy drugs used alone or in combination with radiotherapy must be tested in this pathology.

Acknowledgements

With our acknowledgements to Miss Stéphanie Hurtault.

References


