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CLINICAL TRIAL REPORT

Concurrent radiotherapy: fotemustine combination for newly diagnosed malignant glioma patients, a phase II study

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Abstract
Purpose Fotemustine is a nitrosourea compound used for the treatment of malignant gliomas, especially in France. Recently, an EORTC-NCIC study has shown that a concomitant combination of radiotherapy plus temozolomide (an oral cytotoxic drug) improved survival in glioblastoma patients. We set out to test a concurrent combination of radiotherapy and fotemustine for newly malignant gliomas.
Methods A prospective single-center phase II study opened for accrual in September 2004. Patients over 18 years of age able to give informed consent and with histologically proven, newly diagnosed supratentorial malignant gliomas were eligible. All patients were treated by a standard cranial irradiation (conformal irradiation, tumor bulk plus a margin of 2.5 cm) and concomitant daily administration of 10 mg/m^2 of fotemustine (5 days per week, 6 weeks, 1 h 30 min before radiation therapy). Adjuvant chemotherapy, fotemustine, was administered at tumor progression as standard and classic regimen.
Results Twenty-two patients were enrolled, 16 men and 6 women, median age 56 years (range 32–74), median Karnofsky performance status 70 (range 60–90). Histology included 16 glioblastomas, 3 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas and 1 mixed glioma. Eight patients underwent surgery (three total resections). Fourteen patients had a stereotactic biopsy. The concurrent radiotherapy–fotemustine combination was well tolerated: toxicity was mild and three hematologic toxicities grade 3–4 were observed. Median survival from the initial diagnosis was 9.9 months, two patients are currently alive. Median survival was 11 months for surgery and 9 months for stereotactic biopsy.
Conclusions Concomitant radiotherapy–fotemustine combination is safe and well tolerated. Overall survival of over 10 months for the whole population compares favorably with other reports.

Keywords Malignant gliomas · Concurrent chemotherapy · Nitrosourea · Fotemustine · Radiotherapy

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Introduction

Malignant gliomas account for approximately 60% of all primary brain tumors in adults [1–4]. They can be separated into three types, namely, anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and glioblastoma multiforme (GBM) on the basis of histology. The standard of care consists of surgical resection of as much of the tumor as is considered to be safe, followed by radio- and chemotherapy and has been so for many decades [1–4]. However, despite advances in neurosurgery and radiotherapy, prognosis remains dismal. The median survival for patients with newly diagnosed glioblastoma is 8–15 months, prognosis is slightly better for newly diagnosed grade III glioma with a median survival of 24–36 months, and for anaplastic oligodendrogliomas prognosis gives a median survival of 60 months [1–4].

The reasons for the poor prognosis of malignant gliomas include the ineffectiveness of surgical resection due to the diffuse infiltration of glioma cells into the surrounding brain parenchyma, and the high degree of chemo-resistance of these

tumors giving at best short-lived responses with rapid development of resistance [5]. This resistance is due to genetic transformations and the heterogeneity of this type of neoplasm. Another reason for poor prognosis resides in the fact that the anti-neoplastic agents are largely unable to cross the blood–brain barrier to reach the tumor cells intercalated in the normal brain parenchyma [5]. This, however, is not the case for the smaller lipophilic molecules such as nitrosoureas [5].

A few studies indicate that some human cell lines are sensitive to killing by low radiation doses ($\leq$1 Gy); this has been termed "low dose hypersensitivity" (HRS) [6]. Few works demonstrated that repeated low dose irradiation (ultrafractionation) could greatly improve the effectiveness of radiotherapy on gliomas, and could allow safely treating patients with cumulative doses greater than 60 Gy [6]. Strikingly, experiments conducted on glioma xenografts demonstrated that combination of repeated low doses irradiation (0.8 Gy, thrice a day) with low doses fotemustine is effective to inhibit tumor growth [6]. So, fotemustine could be used as a radiosensitizer agent, it was a novel and promising characteristic [6].

We therefore initiated a phase II clinical trial to test a concurrent combination of radiotherapy and fotemustine, a nitrosourea agent. Standard cranial irradiation was delivered with daily administration of an intravenous perfusion of fotemustine (one and a half hours beforehand), except at weekends. All types of malignant gliomas were included.

Patients and methods

Study objectives

The primary end points of this prospective single-center phase II study were to document treatment-related toxicity and tolerability. Secondary end points were progression-free survival (PFS) and overall survival (OS) of all patients treated with this concurrent radiotherapy–fotemustine combination schedule.

Eligibility

The eligibility requirements were patients $\geq$18 years, with newly diagnosed histologically confirmed supratentorial malignant glioma (WHO classification), a Karnofsky performance status (KPS) $\geq$60, and with an absolute neutrophil count (ANC) $\geq$1,500 cells/ml and a platelet count $\geq$125,000 cells/ml, but with a normal baseline liver, renal, and cardio-function. None of the patients could have received any prior chemo- or radiotherapy. Sexually active women were required to use contraceptive measures for the duration of the treatment. All patients had to be able to give an informed consent and were approved by the institutional review board before entry.

Patients were not eligible if they were in poor medical condition because of malignant systemic disease or acute infection, had infratentorial tumors or an estimated survival of less than 3 months.

Treatment

Radiotherapy consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily 5 days per week (Monday through Friday) over a period of 6 weeks, for a total dose of 60 Gy. Radiotherapy was delivered to the gross tumor volume with a 2-to-3-cm margin for the clinical target volume. Radiotherapy was planned with dedicated computed tomography (CT) and three-dimensional planning systems; conformal radiotherapy was delivered with linear accelerators with nominal energy of 6 MV or more, and quality assurance was performed by means of individual case reviews. Adequate immobilization during therapy and reproducibility was ensured by fitting patients with thermoplastic immobilization masks.

Concomitant chemotherapy, fotemustine, was administered intravenously daily at 10 mg/m^2, 5 days per week from the first to the last day of radiotherapy for 6 weeks i.e. a total of 30 days. Antiemetic prophylaxis with a 5-hydroxytryptamine$_3$ antagonist was recommended before the initial doses of concomitant fotemustine.

Assessments

Patients were assessed weekly during radiotherapy for tolerability and toxicity. The baseline examination included cranial magnetic resonance imaging (MRI) with and without contrast and physical and neurological examination including Mini-Mental-Status score (MMS) and a quality-of-life questionnaire. Baseline examination was performed at the end of the radiotherapy regimen (within the first 10 days after completion of irradiation) and then every 2 months until death. Tumor progression was defined according to the modified WHO criteria as an increase in tumor size by 25% (size of the product of the largest perpendicular diameters of contrast-enhancing tumor), the appearance of new lesions, or an increased need for corticosteroids. When there was tumor progression, patients were treated with fotemustine as induction treatment (one weekly perfusion of 100 mg/m^2 for 3 weeks), and then up to four cycles of adjuvant fotemustine according to the standard regimen of one 100 mg/m^2 perfusion every 28 days after a 4-week break.

Statistical analysis

All variables were described for the whole sample and separately by surgery group. Continuous variables were

described with mean ± standard deviation, categorical variables with percentages.

Survival rates were estimated with Kaplan–Meier analysis. We subsequently analyzed overall survival (OS) and event-free survival (EFS). The log-rank test was used to compare OS, and an EFS univariate analysis was performed to identify which variables had a significance level <0.1 (log-rank test) and included in multivariate analysis.

Results are reported as median and inter-quartile range [Q1–Q3]. The significance level was 0.05. The SAS v8.2 was used for statistical analysis.

Results

Patients

Twenty-two patients, 16 males and six females, were enrolled from September 2004 to October 2006. Histology review identified 16 GBM, 3 AA, 2 AO and 1 mixed glioma. The median age of the patients was 56 years, range 32–74 years; 31.8% of patients were ≥60 years. The median Karnofsky performance status (KPS) was 70, range 60–90. Fourteen patients (63.6%) underwent stereotactic biopsy, five patients subtotal resection (22.7%), and three gross total resections (13.6%). All patients received the planned 60 Gy of radiotherapy. The median time from diagnosis to the start of radiotherapy was 5 weeks (range 2–8 weeks). Unplanned interruption in radiotherapy was brief and due to holidays, radiotherapy equipment maintenance and technical problems.

Safety

Toxicities were evaluated during combined association, and graded according to the National Cancer Institute Common Toxicity Criteria. No toxic death occurred and no radiotherapy regimen was stopped or delayed. The concurrent radio- and chemotherapy was well tolerated. The main side effect was hematologic with myelosuppression. During the treatment, grade 3 and 4 thrombocytopenia occurred in three patients (13.6%) causing suspension of the chemotherapy regimen. Grade ≤ 2 hematologic, especially thrombocytopenia, was reported in seven cases. No ≥ grade 3 nonhematologic toxicity was noted. Few patients developed fatigue (five cases), and experienced nausea (two cases). So, 19 patients completed the course of combined radiotherapy–fotemustine (86.36%).

Survival and progression

The median survival for the whole population was 9.9 months (Fig. 1) (Q1: 9.9 months, Q2: 9.9 months); the median survival for surgery and biopsy was 11 and 9 months, respectively (Fig. 2); the difference was not statistically significant. The median time to progression (TTP) was 6 months (Fig. 3) (Q1: 3.45 months and Q2: 8.38 months for males, and Q1: 5.95 months and Q2: 16.2 months for females). At a follow-up at 3 years, 2 patients remained alive (9%) and 20 patients died (91%). The overall survival at 18 and 24 months was 13.6% (three patients) and 9% (two patients), respectively. The three patients alive at 18 months had undergone a stereotactic biopsy; histology was one GBM, one AA and one OA.

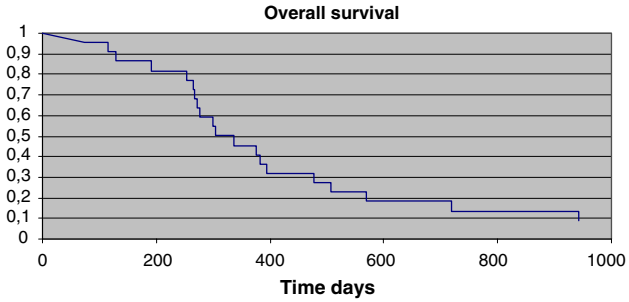

Fig. 1 Overall survival

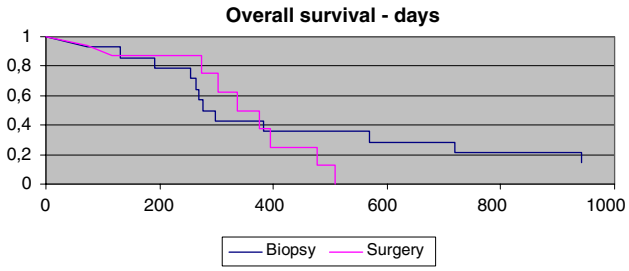

Fig. 2 Survival according to surgery

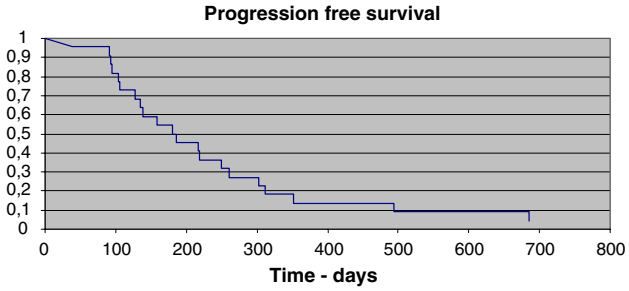

Fig. 3 Time to progression

Response to therapy

Tumor response was analyzed using classic criteria [2]. One complete response (CR) (5%) and two partial responses (PR) (10.5%) were reported giving an overall response rate (CR + PR) of 15.5% (Fig. 4). Stabilization was noted in eight patients (42.1%). Chemotherapy, fotemustine, was administered at disease progression as

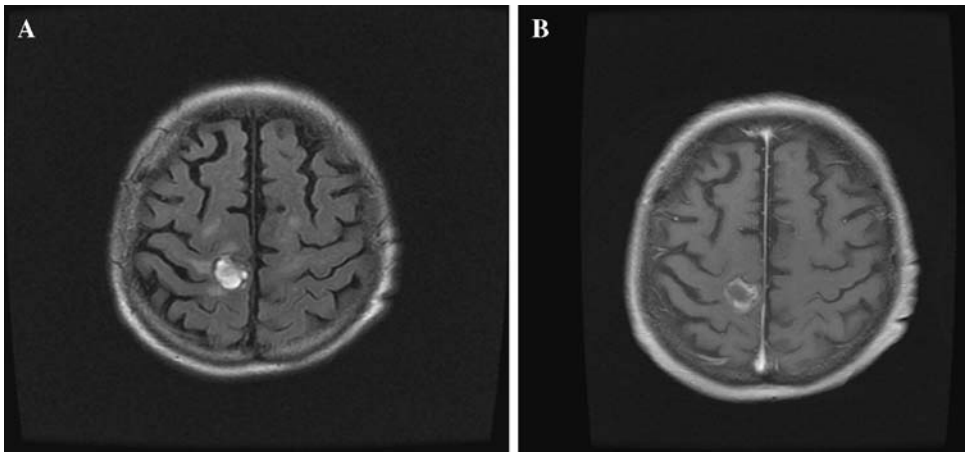

Fig. 4 A long survival patient, with a remission response. Lesion is right parietal. **a** MRI, Flair image **b** MRI, Gadolinium enhanced sequence

previously described. Fifteen patients received fotemustine and one received temozolomide. Temozolomide was administered in seven patients as second line chemotherapy. The response to salvage chemotherapy was not recorded as part of our study.

Discussion

Our concomitant radiotherapy–fotemustine combination is safe and well tolerated. Overall survival of over 10 months for the whole population compares favorably with other reports.

Standard treatment for malignant glioma patients is maximal surgical resection followed by adjuvant radio- and chemotherapy [1–4]. The addition of adjuvant chemotherapy has been controversial; adjuvant therapy with nitrosoureas has been justified by trials and a meta-analysis showing a small long-term survival benefit, especially at 18 and 24 months. These studies showed that there was a 10.1% increase in patient survival over 1 year and an 8.6% increase over 2 years for patients treated with both chemo- and radiotherapy as opposed to those treated with radiotherapy alone [3, 4].

Fotemustine is a chloroethylnitrosourea characterized by a high liposolubility, a low molecular weight, favoring a rapid passage across the blood–brain barrier, and a special chemical structure including an alanine phosphonic ester [7]. Its anti-tumor activity is related to its ability to alkylate DNA and its in vitro or in vivo pharmacological activity is the same as or greater than that of the other nitrosoureas [7–10]. Fotemustine is usually administered at tumor recurrence or after radiotherapy. In monotherapy, the recommended therapeutic regimen is an initial treatment of a 1-hour intravenous infusion of 100 mg/m²/week for three consecutive weeks, followed by a rest period of 4–5 weeks, and then maintenance treatment at the same dosage every 3–4 weeks [10].

Our previous in vivo experiments were encouraging and supported the development of a phase II study [6]. So, a low dose fotemustine regimen was choose and administered in combination of standard cranial irradiation, the induction phase of fotemustine was not justified [6]. Although it was administered concurrently to radiotherapy, our results seem to be similar to data reported in the literature. For recurrent malignant gliomas, Frenay et al. reported a median survival of 10 months, and a response rate of 22.2% in 63 evaluable patients [11]. Silvani et al. reported an overall survival of 7 months and PR 11.2% in patients with recurrent malignant glioma after temozolomide when treated by a salvage combination with procarbazine and fotemustine [12]. Ozkan et al. testing fotemustine after radiation therapy for malignant gliomas, obtained a median survival of 11 months in 27 patients [13]. In another study testing an up-front combination of fotemustine–cisplatin–etoposide before irradiation, Frenay et al. obtained an overall survival of 10 months and an objective response rate of 27% for 33 non-removable glioblastoma patients [14].

Our concurrent combination was well tolerated; the main side effect was hematologic and mild. Thrombocytopenia was the main side effect that could occur with the use of fotemustine. The rate of treatment completion was excellent (86.36%). Although this combination regimen was a constraint to patients, it was well accepted; and the compliance was excellent. The quality of life was not affected; the cost of this combination was similar as the classical treatment combination of radiotherapy and temozolomide. The treatment-related morbidity was not different than radiotherapy and temozolomide.

The standard of care for patients with glioblastoma was defined in a recent report of a phase III randomized trial as radiation therapy with concurrent temozolomide followed by 6 months of temozolomide [15]. Patients who received both radiotherapy and temozolomide had significantly longer overall survival and a significantly higher rate of

2-year survival, than the group treated with radiotherapy alone: survival rates were, respectively, 14.6 and 12.1 months [15]. For patients with non-removable tumors, the difference was not significant with a median survival of 7.9 months for the radiotherapy alone arm and of 9.4 months for the temozolomide/radiotherapy arm [15]. Athanassiou et al. in their phase II study testing a concurrent combination of irradiation and temozolomide for malignant gliomas, reported a median survival of 13.4 months for the combined arm and 7.7 months for the control arm [16]. In a phase III trial of local chemotherapy with biodegradable carbustine (BCNU) wafers (Gliadel), where all patients underwent a tumor resection followed by standard cranial irradiation, the median survival in the BCNU wafer arm and in the control arm was, respectively, 13.9 and 11.6 months [17]. The NCCTG-SOG trial, testing two regimens of radiation therapy (standard irradiation vs. accelerated irradiation), reported a median survival for patients who received BCNU plus irradiation (arms A and B) of 10.1 months versus Cisplatin–BCNU plus radiation therapy (arms C and D) of 11.5 months [18]. Our results seem to be in accordance with the previous reports: adjuvant chemotherapy should thus be recommended.

Curran et al. defined prognostic classes of malignant glioma patients using a recursive partitioning analysis (RPA) of pre-treatment and treatment variables in over 1,500 patients entered on RTOG clinical trials [19, 20]. These classes provide reliable historical controls with which results of phase II studies may be compared [19, 20]. Our population comprised 1 patient of class RPA III, 8 patients of class RPA IV (36.4%), and 13 patients of class RPA V group (59%). For class RPA V, our results are mostly higher than the historical group for median survival and overall survival at 24 months (9 months: 7.7% and 7.4 months: 8%, respectively) [19]. For class RPA IV, the results are similar, 13.1 months: 12.5% and 11.5 months: 17%, respectively [éà].

In conclusion, our phase II clinical trial testing a concurrent radiotherapy and fotemustine combination was safe and well tolerated. Overall survival compares favorably with expected results for malignant gliomas. However, many questions remain unanswered regarding the optimal combination of radiotherapy and fotemustine.

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