Neoadjuvant cisplatin and etoposide, with or without tamoxifen, prior to radiotherapy in high-grade gliomas: a single-center experience

Roberto Díaz[a], María V. Jordá[b], Gaspar Reynés[a], Jorge Aparicio[a], Ángel Segura[a], Román Amador[c], Verónica Calderero[a] and Andrés Beltrán[d]

Neoadjuvant chemotherapy (CT), prior to radical radiotherapy (RT), in the treatment of high-grade gliomas may offer several advantages over standard adjuvant CT. The addition of tamoxifen, which can circumvent P-glycoprotein (P-gp)-mediated chemo-resistance, also merits attention. We have evaluated the neoadjuvant regimen of cisplatin and etoposide after surgery of grade III–IV gliomas and prior to radical RT, with regard to response rates (RRs), overall survival (OS) and time to progression (TTP). The synergistic activity between etoposide and tamoxifen was also studied. Forty-four patients were included. CT regime: cisplatin 100 mg/m^2 on day +1 and etoposide 100 mg/m^2 on days +1 to +3 every 3 weeks for 3 cycles. The initial 24 were also treated with high-dose tamoxifen, 275 mg/m^2 on days −3 to +3. An immunohistochemical analysis of P-gp, p53, vascular endothelial growth factor, Ki67 and bcl-2 was also performed. Median follow-up was 11.57 months. In the 16 patients with measurable disease after surgery, a RR of 12.5% was seen, with 37.5% of disease stabilizations and 31.25% of progressions. The median OS and TTP were 11.3 and 5.7 months. Excluding the three deaths possibly related to tamoxifen, grade 3–4 was low, mainly emesis. Favorable prognostic factors were age less than 60 years, extent of surgery, absence of measurable disease, and the absence of radiological necrosis and ring enhancement. Only high p53 expression was associated with better OS. We conclude that neoadjuvant cisplatin and etoposide is a feasible regime, although any real advantage over standard adjuvant CT is dubious. Short-course high-dose tamoxifen should not be used alongside primary CT. *Anti-Cancer Drugs* 16:323–329 © 2005 Lippincott Williams & Wilkins.

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[a]Medical Oncology Unit, [b]Pathology Department, [c]Radiotherapy Department and [d]Neurosurgery Unit, University Hospital La Fe, Valencia, Spain.

Correspondence to R. Díaz, Medical Oncology Unit, University Hospital La Fe, Avenida Campanar 19–21, 46009 Valencia, Spain.
Tel/fax: +34 96 197 31 38;
e-mail: rdiazbev@hotmail.com

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Introduction

The treatment of high-grade gliomas remains a significant challenge for the physician due to their dismal prognosis, especially for the glioblastoma type. Standard treatment includes maximal surgical resection and adjuvant radiotherapy [1]. The benefit of adjuvant chemotherapy is small, due to the small benefit observed in most studies, the scarceness of truly active agents and the possibility of undue toxicity in this group of patients. The usual way of administration is concomitant with or shortly after adjuvant radiotherapy. The use of chemotherapy prior to radiotherapy, or 'neoadjuvant' chemotherapy, is a novel way of administering chemotherapy which would theoretically allow the identification of truly active agents, without the confounding effects of radiotherapy, with a shorter overall treatment time [2]. Some phase I–II studies have been published with different chemotherapy regimes, with encouraging results with regard to response rates (RRs), although with no clear benefit in overall survival (OS). Of these, the combination of platinum analogs and etoposide has been tested both in the neoadjuvant [3–6] and in the recurrent setting [7–9], with acceptable results and non-overlapping toxicity.

Several *in vitro* studies have shown that tamoxifen can reverse the chemo-resistance induced by the MDR1 gene and its product, P-glycoprotein (P-gp) [10]. P-gp has been shown to bind in the blood–brain barrier (BBB) drugs such as paclitaxel and etoposide, and efflux them back to the systemic circulation [11,12]. Thus, inhibition of P-gp by tamoxifen could also be a valuable therapeutic alternative. Three successive studies [10–12] have shown that the plasma concentration of tamoxifen needed to reverse the resistance *in vitro* mediated by P-gp (3.0 μmol/l) could be achieved with short-course high-dose tamoxifen in the fourth day of treatment. With 320mg/day, 43% of patients achieved that concentration, while with a dosage of 480 mg/day it was achieved in 91% of patients. Higher doses (720 mg/day) did not achieve higher plasma concentrations of tamoxifen, but toxicity was increased greatly, mainly emesis, leukopenia and deep venous thrombosis. With all these results in mind, we undertook a prospective study of neoadjuvant

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chemotherapy and tamoxifen in the treatment of high-grade gliomas.

Thus, we present the long-term results with regard to RRs and OS of our series of high-grade glioma patients treated with neoadjuvant chemotherapy with cisplatin and etoposide. In the first 24 patients, short-course high-dose tamoxifen concomitant with chemotherapy was added. We also measured by immunohistochemistry the P-gp expression, as well as the expression of other well-known molecular factors, such as p53, Ki-67, bcl-2 and vascular endothelial growth factor (VEGF), in the tumor samples. Finally, we also report the toxicity of the regime, and a separate analysis of pre-treatment clinical, radiological and pathological prognostic factors.

Material and methods

This study is an open-labeled, single-arm, single-center phase II trial, designed to assess the efficacy and toxicity of pre-irradiation chemotherapy with cisplatin and etoposide with the addition of high-dose tamoxifen.

To be eligible for this study, all patients were required to have histologically proven newly diagnosed glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA), with no history of previous brain irradiation and/or chemotherapy. Other eligibility criteria were: age > 18 years, Karnofsky performance status $> 60\%$, normal hematologic counts (absolute neutrophil count $> 1500/\mu l$, platelet count $> 100\,000/\mu l$), and acceptable renal (blood urea nitrogen and creatinine ≤ 1.5 times the upper limit of laboratory normal values) and hepatic (serum bilirubin ≤ 1.5 mg/dl) function. All patients were enrolled after giving informed consent.

After surgery, all patients were evaluated within 72 h with brain computed tomography (CT) or, preferably, brain magnetic resonance imaging (MRI), to evaluate for measurable disease; patients were required to be on a stable or decreasing dosage of steroids for more than 72 h before baseline neuroimaging. A comprehensive physical and neurological examination was also performed to serve as baseline for future examinations.

Chemotherapy was administered 3 weeks after initial surgery. It consisted of cisplatin 100 mg/m^2 on day $+1$, and etoposide (VP-16) 100 mg/m^2 on days $+1$, $+2$ and $+3$, in 3-weekly cycles, for a maximum of 3 cycles, or less if unacceptable toxicity or disease progression developed. In the initial 24 patients, high-dose tamoxifen at a daily dosage of 275 mg/m^2 was also given on days -1, -2, -3, $+1$, $+2$ and $+3$, for a total of 6 days every cycle, coinciding with the chemotherapy. No prophylaxis against deep venous thrombosis (DVT) was given. A clinical evaluation, full blood count and basic biochemistry were performed on all patients before each cycle; the dosage of steroids was also noted. After 3 cycles, or less in the case of suspected disease progression, a CT or MRI scan was performed, and the MacDonald criteria were used to evaluate response.

After chemotherapy, radical radiotherapy was begun with a standard fractionation scheme (1.8–2 Gy/fraction once a day for 5 days weekly), with an initial dose of 40 Gy in a volume covering the contrast-enhancing lesion and surrounding edema (with a 3-cm margin), and an additional 20 Gy to the contrast-enhancing lesion alone (with a 1-cm margin), for a total dose of 60 Gy. Megavoltage techniques with multiple port fields were designed. Clinical evaluation was performed weekly during radiotherapy; after its end, CT or MRI was performed to evaluate for response. After completion of radiotherapy, adjuvant chemotherapy with the alkylating agent BCNU (in the GBM patients) or the PCV polychemotherapy regimen of procarbazine, vincristine and lomustine (in the AA patients) was given for 6 cycles.

The WHO Common Toxicity Criteria were used in case of toxicity attributed to chemotherapy, while the joint Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment (EORTC) toxicity criteria were used in case of suspected radiation-induced toxicity.

The primary end-point was OS. Secondary end-points were time to progression (TTP), RRs and toxicity rates. TTP was defined as the period of time from the date of surgical resection that confirmed the diagnosis of high-grade glioma to the date of the first progression of disease, while OS was measured from the date of surgical resection to the moment of death.

All tumor samples were analyzed by two pathologists from our center. The WHO histological criteria were used to define GBM (grade IV glioma) and AA (grade III glioma). In 41 of the 44 patients, a complete immunohistochemical study of the expression of different tumor markers (p53, bcl-2, Ki67, endothelial P-gp, cellular P-gp and VEGF) could be performed. Due to the continuous nature of the cellular expression of the different markers, for statistical purposes, the expression for all markers was divided in three groups: low expression ($< 10\%$ of cells), medium expression (10–50% of cells) and high expression ($> 50\%$ of cells), except for P-gp, where it was classified as low ($\leq 10\%$ of cells) and high expression ($> 10\%$ of cells).

The product-limit method of Kaplan–Meier was used to define OS and TTP, while the differences between OS curves according to different clinical, neuroradiological and immunohistochemical prognostic factors were analyzed by the log-rank test. The statistical analysis was

performed in March 2004. All calculations were performed using the SPSS 10 software package (SPSS, Chicago, IL).

Results

Forty-four patients were included between March 1996 and January 1998. Clinical and neuroradiological characteristics are shown in Table 1. The immunohistochemical results obtained in 41 patients are shown in Table 2.

All patients received chemotherapy as per protocol with cisplatin and etoposide, and the initial 24 patients were also treated with high-dose tamoxifen; however, the perceived higher toxicity rate observed led us to discontinue its use in the last 20 patients. A total of 94 cycles of chemotherapy were given, with eight patients (18.2%) receiving 1 cycle, 20 patients receiving 2 cycles (45.5%) and 16 patients receiving 3 cycles (36.4%). Grade 3–4 toxicity observed was emesis in 16 cycles (17.1%), anemia in 3 cycles (3.2%), thrombocytopenia in 1 cycle (1.1%) and neutropenia in 4 cycles (4.25%); two cases of DVT were observed in the arm treated with tamoxifen. Three deaths possibly related to treatment were observed, all in patients treated with tamoxifen: a patient with pneumonia in grade 4 neutropenia after the third cycle, a patient with a bilateral pneumonia, but no neutropenia, after the third cycle and a patient with a possible pulmonary embolism after the first cycle of chemotherapy.

Sixteen patients with measurable disease after surgery were evaluable for response to chemotherapy. A RR of 12.5% was observed (6.25% complete responses and 6.25% partial responses), with 37.5% of disease stabilizations and 31.25% of disease progressions during treatment; three patients (18.7%) were not evaluable, as two were toxic deaths and the other patient refused to continue with chemotherapy. In the remaining 28 patients with no measurable disease after surgery, 16 (57.14%) did not progress during treatment, while 10 did progress (35.71%) and radiotherapy was begun early; two (7.14%) were not evaluable, as chemotherapy was halted early due to unacceptable toxicity.

Nine patients in total (20%) did not receive radiotherapy due to the three toxic deaths described earlier and to progressive disease during chemotherapy which worsened the performance status of the patients. The definitive responses to radiotherapy are shown in Table 3. Adjuvant chemotherapy was given to 29 patients (65.9%), with BCNU in 25 patients and PCV in the remaining four patients. The median number of second-line chemotherapy cycles was 2 (range 1–6); the responses to adjuvant chemotherapy were progressive disease in 16 patients (55.18%), complete response in three patients (10.34%), partial response in one patient (3.45%) and stable disease in four patients (13.8%); the remaining five patients were not evaluable. Two treatment-related deaths were observed during second-line chemotherapy with BCNU and PCV.

With a median follow-up of 11.57 months, nine patients are still alive. The median OS is 11.27 months (Fig. 1), while the median TTP is 5.67 months (Fig. 2). In the univariate analysis, the extent of surgery ($p = 0.010$), the

Table 1 Patient's clinical and neuroradiological characteristics ($n = 44$)

Age (years) [median (range)]	58 (21–70)
≥ 60 years [*n* (%)]	17 (38.6)
<60 years [*n* (%)]	27 (61.4)
Sex [*n* (%)]	
male	25 (56.8)
female	19 (43.2)
Postoperative Karnofsky PS [*n* (%)]	
≥ 80	24 (54.5)
<80	20 (45.5)
Symptoms at diagnosis (yes/no) [*n* (%)]	
headache	21/23 (47.7/52.4)
convulsions	11/33 (25/75)
neurological focality	30/14 (68.2/31.2)
low conscience level	16/28 (36.4/63.6)
Surgery performed [*n* (%)]	
open biopsy	4 (9.1)
stereotactic biopsy	6 (13.6)
partial resection	3 (6.8)
subtotal resection	14 (31.8)
total resection	14 (31.8)
lobectomy	3 (6.8)
Measurable disease after surgery [*n* (%)]	
yes	16 (36.4)
no	28 (63.6)
Side [*n* (%)]	
right-sided	23 (52.3)
left-sided	20 (45.5)
bilateral	1 (2.3)
Histological diagnosis [*n* (%)]	
GBM	36 (81.8)
AA	8 (18.2)
RTOG prognostic group [*n* (%)]	
I	3 (6.8)
II	0 (0)
III	6 (13.6)
IV	15 (34.1)
V	17 (38.6)
VI	3 (6.8)
Ring enhancement [*n* (%)]	
yes	13 (29.5)
no	30 (68.2)
unknown	1 (2.3)
Radiological necrosis [*n* (%)]	
yes	32 (72.7)
no	8 (18.2)
unknown	4 (9.1)
Cyst formation [*n* (%)]	
yes	21 (47.7)
no	21 (47.7)
unknown [*n* (%)]	2 (4.5)
Edema	
none	3 (6.8)
+	20 (45.5)
+ +	12 (27.3)
+ + +	7 (15.9)
unknown	2 (4.5)
Mass effect [*n* (%)]	
yes	38 (86.4)
no	4 (9.1)
unknown	2 (4.5)

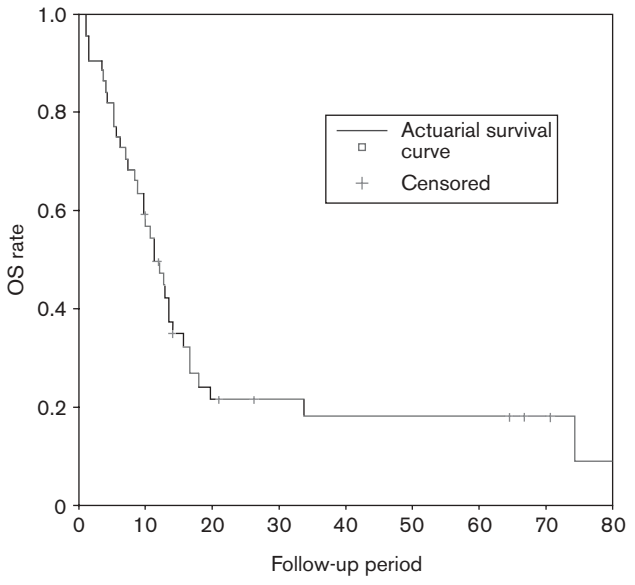
Table 2 Immunohistochemical analysis of tumor samples ($n=41$)

VEGF [*n* (%)]	
low expression	6 (14.6)
medium expression	16 (39)
high expression	19 (46.3)
p53 [*n* (%)]	
low expression	13 (31.7)
medium expression	24 (58.5)
high expression	4 (9.8)
bcl-2 [*n* (%)]	
low expression	28 (68.3)
medium expression	9 (22)
high expression	4 (9.8)
Ki67 [*n* (%)]	
low expression	2 (4.9)
medium expression	7 (17.1)
high expression	32 (78)
Cellular P-gp [*n* (%)]	
low expression	35 (85.4)
high expression	6 (14.6)
Endothelial P-gp [*n* (%)]	
low expression	18 (43.9)
high expression	23 (56.1)

Table 3 Tumor responses after radiotherapy ($n=35$)

Complete responses	8 (22.85%)
Partial responses	3 (8.57%)
Stable disease	3 (8.57%)
Progressive disease	20 (57.15%)
Not evaluable	1 (2.85%)

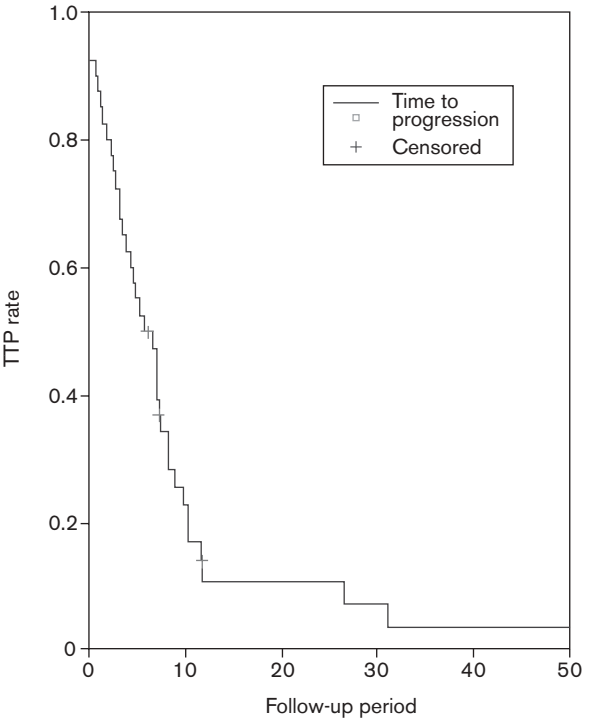
Fig. 1



OS curve, according to the Kaplan–Meier method.

absence of measurable disease ($p = 0.035$) and age lower than 60 years ($p = 0.0148$) were significantly related to a longer survival, while a low conscience level as initial

Fig. 2



TTP survival curve, according to the Kaplan–Meier method.

symptomatology ($p = 0.035$) and the presence of radiological signs of necrosis (p 0.0391) and ring enhancement ($p = 0.0352$) were associated with a poorer prognosis. Karnofsky performance status higher than 80 had a borderline favorable statistical significance ($p = 0.0616$). No relationship was observed with regard to sex, location or size. Of all the immunohistochemical parameters, only high expression of p53 was associated statistically with a better survival rate ($p = 0.0344$).

Discussion

The outcome of patients with high-grade gliomas has remained virtually unchanged in the last three decades. For adults with GBM, the median survival time remains less than 1 year, survival at 2 years is less than 10% and long-term survival is rare [1]. Standard treatment at this time would include surgical resection and postoperative external-beam radiotherapy [1]. Although chemotherapy has a small albeit significant role in the recurrent setting, the benefit seen in the adjuvant setting is small, with a modest benefit in two meta-analysis and in some randomized studies [13,14], but not in others [15] (however, its value is well established for the group of patients with AA [16]). Few agents have documented efficacy, and they include the nitrosureas, procarbazine and temozolamide, which yield RRs of 20% or less in the recurrent setting [17,18]; other agents that have been

studied include the platinum analogs, etoposide and paclitaxel, although the RRs have been lower [19–21]. If adjuvant chemotherapy is to be used, the traditional approach is to start postoperative treatment with radiotherapy, followed by chemotherapy, with the aim to eliminate persistent tumor cells after irradiation [2].

The use of neoadjuvant chemotherapy, as in our study, has the theoretical advantages of allowing us to evaluate its RRs without the confounding effects of radiotherapy and of greatly enhancing the discovery of truly active agents in this setting [2]. Surgery-induced changes in the tumor microvasculature, with an increase in the BBB permeability, may also enhance the effectiveness of the chemotherapy given. In our case it was decided to administer neoadjuvant cisplatin and etoposide, two agents widely used in the treatment of high-grade gliomas, with a synergistic effect *in vitro* and *in vivo*. In addition, each has a different toxicity profile, which allows them to be given in combination [7–9].

The use of tamoxifen in high-grade gliomas is controversial. Glioma cells have high levels of protein kinase C (PKC; an enzyme for mitogenic signal transduction) compared to normal astrocytes [22]. Tamoxifen at high doses (above 160 mg/day) has non-specific PKC inhibitor properties, which may justify its effectiveness in preclinical studies [22,23]. Tamoxifen also acts as a MDR reversal agent (multidrug resistant gene, of which the product is P-gp) [10]. The capillary endothelial cells in the BBB express high amounts of P-gp, which binds drugs like paclitaxel and etoposide, and effluxes them back into the systemic circulation. In animal models, pre-treatment with tamoxifen increased penetration and deposition of drugs like etoposide into glioma tissue [11,12]. In some phase II studies in patients with recurrent high-grade gliomas, monotherapy with high-dose tamoxifen (160–200 mg/m^2) has shown acceptable results, with RRs of around 20%, mainly in the form of stabilizations, with low toxicity overall [24,25]. Unfortunately, the use of tamoxifen alongside standard treatment with radiotherapy and/or chemotherapy in the first-line setting has shown disappointing results, with little benefit with regard to response and survival rates, and higher rates of toxicity, mainly hematological and thrombosis related [26–28]. These results mirror those of our study, where the toxicity rate was deemed unacceptably high and the use of tamoxifen was stopped early. Thus, there is little support at the moment for the use of tamoxifen in the treatment of high-grade gliomas.

Our patients would be considered a poor-prognosis group, with a predominance of patients in the class IV and V of the RTOG prognostic groups, with median survival rates of 12 months and 2-years survival rates of only 10–15% [29]. Only 18.2% were AAs. The analysis of pre-treatment prognostic factors in our study shows statistical significance for well-established clinical prognostic factors, such as age, extent of surgery and the absence of low conscience level as initial symptomatology, although the small number of patients included makes any generalizations difficult to assess [30,31]. Of note, the radiological presence of necrosis and ring enhancement, typical radiological features of glioblastoma, show statistical significance, as would be expected. Of all the immunohistochemical parameters studied, only high expression of p53 was found to have a positive effect in OS rates. The significance of this finding is uncertain as both high [32] and low [33–35] expression of p53 have been linked to improvement in survival rates in different studies in high-grade gliomas; these discrepancies may be secondary to different cut-off values and methods used in the evaluation of p53 expression [36]. However, it is probable that the influence of p53 expression as a prognostic factor is marginal at best, especially in relationship with other well-established clinical prognostic factors.

With regard to RRs to chemotherapy, in the group with measurable disease after surgery, a 12.5% response was observed, with 37.5% of disease stabilizations; 31.3% of patients progressed during chemotherapy treatment. In the group with no measurable disease, only 35.71% progressed during chemotherapy treatment and radiotherapy was begun early, with no apparent unfavorable effects. Most were treated with 2 or 3 cycles. The median OS rate and progression-free survival rate were 11.27 and 5.67 months, in line with what would be expected in this poor-prognosis group of patients treated in a standard manner. Six patients in total (13.64%) are long-term survivors, half of which are in the AA group, who would be expected to benefit more from the use of adjuvant chemotherapy. Except for the three possibly treatment-related deaths in the arm treated with tamoxifen, the toxicity rate was also quite favorable, mainly emesis grade 3–4 (17.1%).

Compared to our study, the RRs observed in the different phase I–II studies with neoadjuvant chemotherapy show varying response figures [6–9,37–42], from the 42% observed with continuous infusion BCNU and cisplatin in the study by Grossmann *et al.* [37] to the 0% with paclitaxel in the study by Fetell *et al.* [41]. The lower RRs with our chemotherapy regime probably reflect the use of cisplatin and etoposide, two agents with lower intrinsic activity than the nitrosureas and temozolamide (Table 4). However, despite these differing RRs, none of these studies with chemotherapy prior to radiotherapy, including our own, seem to adversely affect survival in these patient populations compared to similar populations treated in the standard manner.

Table 4 Selected studies of neoadjuvant chemotherapy in the treatment of high-grade gliomas

Reference	CT	Histology	*n*	RR (%) (CR/PR/SD/PD)	OS (months)	DFS (months)
Gruber *et al.*, 1998 [6]	CBDCA	glioblastoma	25	NR	19	8.5
Rajkumar *et al.*, 1998 [7]	cisplatin, BCNU, VP-16	malignant glioma	16	0/22/77/11	14	13
Jeremic *et al.*, 1999 [8]	CBDCA, VP-16	malignant glioma	45	0/24/65/11	14	12
Lassen *et al.*, 1999 [9]	cisplatin, BCNU, VP-16	glioblastoma	29	0/33/41/26	11.4	7.6
Grossman *et al.*, 1997 [37]	BCNU, cisplatin	malignant glioma	52	0/42/53/4	13	NR
Dazzi et al, 2000 [38]	BCNU, cisplatin	malignant glioma	13	23/30/NR/NR	9	NR
Gilbert *et al.*, 2000 [39]	cisplatin, BCNU	glioblastoma	41	2.4/24/44/29.6	9.3	5.2
Viñolas *et al.*, 2002 [40]	CBCDCA, CFM	malignant glioma	17	0/6.5/13.5/80	7.6	NR
Fetell *et al.*, 1997 [41]	paclitaxel	glioblastoma	33	0/0/12/88	12	NR
Balaña *et al.*, 2001 [42]	cisplatin, TMZ	glioblastoma	14	11/56/22/1	NR	NR

CT=chemotherapy regime, *n*=number of patients evaluable, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, OS=overall survival, DFS=disease-free survival, CBDCA=carboplatin, VP-16=etoposide, CFM=cyclophosphamide, TMZ=temozolamide, NR=not reported.

Only a phase III trial has been published with regard to the value of neoadjuvant chemotherapy. Grossmann *et al.*, on behalf of the Eastern Cooperative Oncology-Group/ Southwest Oncology Group, randomized 219 patients with newly diagnosed GBM between standard adjuvant BCNU and radiotherapy and neoadjuvant chemotherapy with 72-h infusion of BCNU and cisplatin for 3 cycles, prior to radiotherapy, as in the previous phase II studies [43]. The results were disappointing. Twenty-four percent of patients progressed during chemotherapy. No differences were seen with regard to OS (11.2 versus 11 months) or 1-year survival rates (45 versus 44%). Toxicity was higher in the experimental arm. The authors concluded that the high RRs observed in the phase II setting did not translate in a meaningful survival benefit.

The value of neoadjuvant chemotherapy thus seems unclear. Although RRs vary widely depending on the chemotherapy used, no significant benefit (or detriment) has been observed in relationship to survival rates compared to controls with standard treatment with adjuvant chemotherapy. It seems that, more than the benefit of neoadjuvant chemotherapy, what is still in question is the benefit of chemotherapy in general in the first-line treatment of high-grade gliomas.

High-grade gliomas, and especially GBM, are aggressive diseases, whose prognosis depends more in large part in a series of well-known clinical prognostic factors than in any new treatment modality that can be offered to these patients [2–4]. Apart from adjuvant radiotherapy whose value is well established [1], progress with chemotherapy has been small. The worth of adjuvant chemotherapy rests basically in two meta-analyses [16,17], which showed a modest survival benefit with adjuvant treatment with BCNU, one of them only in young patients, and a slight increase in the number of long-term survivors. There are no known parameters that can predict which patients will benefit from its use [44]. Also, the toxicity of combination adjuvant chemotherapy can be substantial in phase III trials (65% of patients in the Grossmann trial suffered grade 3–4 toxicity) and its indication must be weighed carefully. Moreover, the recent Medical Research Council randomized study in high-grade gliomas, showing no benefit to adjuvant PCV alongside radiotherapy, has cast more doubts on the real value of adjuvant chemotherapy in glioblastoma [8]. However, the preliminary recent findings by Stupp [45] on the benefit of early concomitant and adjuvant temozolamide compared to standard radiotherapy alone seem to show that the highest benefit of chemotherapy could be seen with its early use after surgery, rather than its use after radiotherapy. In this regard, neoadjuvant chemotherapy may offer some theoretical advantages, especially with regard to discovering more active agents, but its real value and possible advantages still have to be determined.

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