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Clinical Study

Treatment of supratentorial glioblastoma multiforme with radiotherapy and a combination of BCNU and tamoxifen: a phase II study

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Comments

Napolitano et al. show by comparing three consecutive phase II trials that the addition of tamoxifen to BCNU does not prolong survival nor time to recurrence. The message is interesting despite the fact (acknowledged by authors) that the doses of tamoxifen used in this study were low.

In addition, this study does not avoid the usual caveats of comparing uncontrolled phase II studies even when performed by the same investigators. For instance, the dose of BCNU actually given to group A (treated only by BCNU) was substantially higher: 700 mg/m^2 than in group B (488 mg/m^2) and group C(500 mg/m^2). Thus the lack of tamoxifen activity could be actually related to lower combined dose of BCNU. This should be specified in the discussion.

Also, the number of patients per group (21–25) is small and the risk of β error is high; this also should be mentioned.

Dr. J.G. Hildebrand (Brussels, Belgium)

This is a nice phase II study report evaluating tamoxifen as part of the initial management of glioblastoma multiforme. Unfortunately, at the doses tried, there was no evident advantage, as had been seen in laboratory evaluation of tamoxifen, and as had been noted in treatment of recurrent gliomas. Toxicities were acceptable, with no new problems not previously identified.

Additional investigations into protein kinase C inhibition may prove fruitful; whether novel toxicities or increased frequencies of known toxicities with higher dose tamoxifen may produce this drug's use require additional investigations.

Prof. J. Knisely (New Haven, CT, USA)

Napolitano and his colleagues reported well-prepared manuscript with a good eligibility for patients. Description in the sections on material and methods and discussion was excellent. All parameters were well observed during their study. Unfortunately, this phase III study with TMX and BCNU failed to show clinical merits. As pointed in this article, dose of TMX might be low. Reviewer questioned if there might be a better procedure to deliver TMX into the residual tumor or into the tumor cavity.

Dr. D. Yoshida (Tokyo, Japan)

Summary

From May 1990 to November 1994, 70 consecutive patients suffering from glioblastoma multiforme were treated following surgery with conventional radiotherapy and adjuvant IV BCNU administered alone or in combination with tamoxifen. Twenty-five patients received BCNU alone (control group A) while 24 patients also received 40 mg of tamoxifen (TMX) PO daily (group B) and 21 received 100 mg of TMX PO daily (group C). There were no significant differences between the 3 groups concerning age, type of resection and median post-operative Karnofsky performance status (KPS). Blood toxicity over grade II occurred in 33.5% of patients receiving TMX versus 12% of patients treated with BCNU alone ($p < 0.05$).

Deep venous thrombosis complications were observed in 4 patients of each TMX group, whereas they were not observed in the control group ($p < 0.04$). Median time to tumor progression (MTTP) was 35 weeks in the control group and 27 weeks in both TMX groups B and C. Median survival time (MST) was 56, 66 and 51 weeks, respectively.

These results suggest that the addition of TMX to standard treatment of glioblastomas does not affect the time to tumor progression and overall survival but may increase the risk of deep venous thrombosis or nitrosourea-induced blood toxicity.

Introduction

The prognosis of glioblastoma multiforme (GBM) remains grim with a median survival of approximately one year despite standard treatment with surgery, radiotherapy, and nitrosourea-based chemotherapy [1–4]. These poor results as well as a better understanding of the mechanisms underlying carcinogenesis, have led many investigators to develop new therapeutic approaches. Since proliferation of human malignant glioma cells depends in part upon the high activity of PKC [5–7], the effect of PKC inhibitors has been tested *in vitro* with encouraging results [8]. Tamoxifen (TMX), a well-known antiestrogen agent, is also believed to inhibit PKC. At concentrations within the nanomolar to micromolar range, which can be obtained in the clinical situation, TMX was found to inhibit proliferation of glioma cell lines [9–12] and to induce objective response in some patients with recurrent high grade gliomas [14,15].

These preliminary results and the observation that TMX could potentiate the effect of radiation therapy on malignant glioma cell lines [13], prompted us to use this agent in an adjuvant setting in combination with the standard treatment of GBM.

Patients and methods

Eligibility criteria

The following criteria were required to enter the study: (1) A histologically proven GBM according to the 1993 WHO classification. (2) No previous treatment save for surgery and anticonvulsants or corticosteroids as needed. (3) Age between 18 and 75 years. (4) A Karnofsky performance status (KPS) superior or equal to 60. (5) No previous history of venous thombosis. (6) Adequate bone marrow function (WBC $> 3.5 \times 10^9/mm^3$, hemoglobin > 10 mg/dl, and platelets $> 130{,}000$). (7) Adequate liver (serum bilirubin < 1.5 mg/dl) and renal functions (serum creatinine < 1.5 mg/dl).

Study population

Between May 1990 and November 1994 (a 54-month period), three groups of eligible patients with GBM were consecutively treated within a month after surgery. After being informed of the study, all patients received a course of conventional radiotherapy delivering a dose of 55–62 Gy with 1.8 Gy per fraction administered to a limited field (including the tumor bed with a 3 cm margin).

The first course of adjuvant chemotherapy was started immediately before the onset of radiotherapy. During the first 18-month period, patients received adjuvant BCNU alone, (group A). During the second (group B) and third (group C) consecutive 18-month periods, patients received adjuvant treatment with BCNU and TMX also started before RT (40 mg/day in group B, and 100 mg/day in group C) (Table 1). Compliance to the treatment was regularly checked (at each course of BCNU) by questioning the patient and close relatives.

Table 1. Patients and treatment characteristics in the three groups

	Group A BCNU alone	Group B BCNU + TMX 40 mg	Group C BCNU + TMX 100 mg	Total
Patient characteristics				
Number of patients	25	24	21	70
Sex M/F	19/6	13/11	19/2	51/19
Median age (range)	56 (38–73)	58 (40–71)	54 (33–70)	56
Median post-operative KPS (range)	90 (60–100)	90 (60–100)	90 (60–100)	90
Treatment characteristics				
Surgery				
Biopsy	8%	0%	14.3%	7.1%
Gross macroscopic resection	64%	62.5%	47.6%	58.6%
Partial resection	28%	37.5%	38.1%	34.3%
Median dose RT(Gy)	60	60	60	60
Median total dose BCNU (mg/m^2)	700	488	500	560
Surgery/RT delay (wk)	3.9	3.9	4	3.9
Surgery/CT delay (wk)	1.4	1.8	1.9	1.70

KPS = Karnofsky performance status, RT = radiotherapy, CT = chemotherapy, wk = weeks.

Scheme of the study

BCNU was delivered intravenously (IV) at a dose of 150–200 mg/m^2, according to hematologic tolerance. Courses of therapy were repeated every 8 weeks, with a maximum of 6 courses. TMX was administered per os daily, until recurrence.

Neurological status and tolerance were judged on clinical examinations repeated at each course of treatment. Therapeutic effect was judged using KPS rating and CT examinations repeated every 8 weeks. Because a post-operative CT scan within 24–78 h after surgery was not always performed, we did not evaluate the rate of response. Median time to tumor progression (MTTP) was calculated from the time of surgery to the time of treatment failure. An increase of over 25% in the largest cross-sectional area of contrast enhancement on CT scan or an increase of steroid dose over 40 mg of equivalent dose of methylprednisolone, was considered a treatment failure. Median survival time (MST) was calculated from the time of surgery to the time of death. WHO scale toxicity criteria were used, and toxicity grades were measured during each cycle and reflected the most severe degree.

Results

Seventy patients were included in this trial. The main characteristics of the 3 groups are indicated in Table 1. There were 51 men and 19 women, aged 33–73 years, (median 56) who received (1–6) courses of BCNU (mean, 3).

Tolerance

Vomiting was prevented by systematic administration of ondansetron before the administration of chemotherapy.

Blood toxicity over grade II occurred in 18 patients (25.8%) (Table 2), including,

- leucopenia in 10 patients (14.3%) (1 patient in group A (BCNU alone) versus 6 in group B (tamoxifen, 40 mg/day) and 3 in group C (tamoxifen, 100 mg/day);
- thrombopenia in 16 patients (22.9%) (3 patients in group A versus 7 and 6 in groups B and C, respectively).

When the two TMX groups were combined, grades III and IV hematotoxicity occurred in 15 patients treated with TMX (33.5%) as compared with 3 patients (12%) in the control group, ($p = 0.05$). A significant ($p = 0.04$) increased risk of venous thrombosis was found in patients treated with tamoxifen when compared to the control group. In group B, 4 patients developed a deep venous thrombosis (DVT) after 2, 4, 6 and 7 months of TMX, respectively. In group C, 3 patients developed a DVT after 4, 4 and 6 months of TMX and another one developed a DVT associated with a pulmonary

embolism after 8 months of TMX. In all cases thrombotic events were treated with anticoagulant therapy and TMX was discontinued. No thrombotic events were observed in group A (details in Table 2).

Therapeutic effects

Median time to tumor progression

The calculated MTTP was 34.5 weeks for group A, 27 weeks for group B and 27 weeks for group C, respectively.

Median survival

MST was 56 weeks in group A and 66 and 51 weeks, respectively in group B and C (58 weeks when both TMX groups were pooled). Figure 1.

Discussion

Tamoxifen has been used in a large variety of malignancies other than breast and endometrial cancers and antitumor effects unrelated to estrogen receptor competition have been observed [16]. The primary mechanism of TMX effect in estrogen-negative tumors is the inhibition of PKC, although interference with calmodulin, mdr 1 protein-mediated drug resistance, or enhancement of the cytotoxicity of other drugs such as cisplatin have also been incriminated [18–23]. The *in vivo* expression of PKC in malignant astrocytomas remains controversial [12,17,24], but some studies in various tumors, including established malignant glioma cell lines, have found that micromolar concentrations of TMX in a range varying from 0.5 to 10 μg/ml were required to inhibit cell proliferation, to induce a cytotoxic effect and to inhibit PKC [8,12]. Close figures

Table 2. Number of patients (%) with hematological toxicity (grade III + IV) and thrombotic complications

	Group A BCNU alone	Group B BCNU + TMX 40 mg	Group C BCNU + TMX 100 mg	Total B + C	p(A/B + C)
Hematotoxicity	3 (12%)	9 (37.5%)	6 (28.9%)	15 (33.5%)	$p = 0.05$
WBC < 1900	1 (4%)	6 (25%)	3 (14.5%)	9 (20.1%)	
Platelets < 49,000	3 (12%)	7 (29.1%)	6 (29%)	13 (29%)	
Thrombophlebitis	0	4 (17%)	4 (19%)	8 (18%)	$p = 0.04$

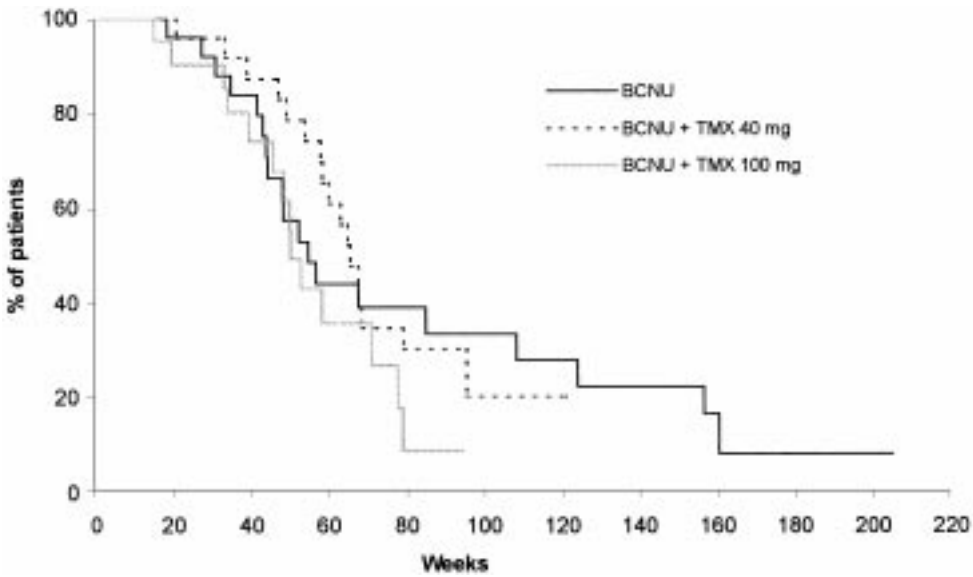

Figure 1. Survival analysis (Kaplan–Meier). There was no significant difference between the three groups.

can be reached in the clinical setting since steady state serum levels of TMX around 0.5 μM have been found in patients treated chronically for breast cancer with doses ranging from 20 to 60 mg/day [25–28]. Based on these findings, Vertosick et al. tested a 40 mg dose of TMX daily in a series of 32 patients with recurrent high grade gliomas.

Tolerance was good and 2 objective responses with 5 stabilizations were observed [14]. These encouraging findings in recurrent tumors as well as preclinical evidence indicating both a dose response effect [15] and radiosensitizing properties of TMX [13] led us to test the possible benefit of escalating doses of TMX (40 and 100 mg/day) administered in an adjuvant setting in combination with radiotherapy and BCNU in patients with GBM.

Unfortunately, our data indicate that both MTTP and MST were comparable in the control and in the TMX groups without evidence for a dose response effect in the TMX groups. Even if our study was not randomized (it was a consecutive series of patients), a major bias is unlikely to account for the apparent lack of effect of TMX since the 3 groups were similar in terms of key prognosis factors including histology (all had a GBM), age and post-operative Karnofsky performance status (Table 1). Another possible explanation for our negative findings is that the doses of TMX were too low.

Indeed, recent data suggest that doses of TMX up to 150 mg/m^2 twice daily, i.e. a dose approximatively 5–10 fold higher than ours, could be much more effective in recurrent malignant gliomas [15,29,30,31]. In this perspective, additional trials using higher doses of TMX in the adjuvant setting could be more rewarding if tolerance remains acceptable. In this study, the overall tolerance to TMX was good with two exceptions concerning the risks of hematological toxicity and DVT.

Blood toxicity of grade III or IV (without toxic death) consisting either of leucopenia and/or thrombocytopenia affected 15 patients treated with TMX and BCNU (33.5%) as compared with 3 patients (12%) in the control group who received BCNU alone ($p = 0.05$).

The reason for this increased toxicity are unclear. By itself TMX can occasionally be responsible for a thrombocytopenia or much more rarely a leucopenia in 3–5% of patients treated with a dose of 20–30 mg/day [32–33]. However, the frequency of blood toxicity that we observed was clearly higher suggesting that the combination of BCNU and TMX was the culprit, in agreement with previous reports that also found increased myelosuppression when TMX (30 mg/day or 150 mg/m^2 twice a day) was combined with a polychemotherapy regimen in patients with breast cancer or advanced refractory malignancies [34,35]. Increased blood toxicity of the TMX–BCNU combination explains that patients receiving both treaments received a lower dose of BCNU (488 and 500 mg/m^2 in groups B and C, respectively), which was administered at reduced doses in subsequent courses, as compared with patients who received BCNU alone (700 mg/m^2).

In addition to blood toxicity, a significant ($p = 0.04$) increased frequency of DVT was identified in the TMX groups as compared with the control group. The episodes of DVT were delayed, occurring 2–7 months (mean, 5 months) after the onset of TMX and responded to anticoagulants and discontinuation of TMX. These results are in agreement with previous studies showing that DVT is the major complication of TMX [32,36,37] through the effect of this drug on blood coagulation [38–41].

Furthermore, the presence of malignant glioma itself is a well-known predisposing factor for DVT, probably linked to the secretion of procoagulant factors by the tumor [42]. These observations raise the question of a role for anticoagulant prophylaxis in patients who receive high dose TMX for GBM. Finally, we did not observe either the retinal toxicity or the neurotoxicity that have been reported after prolonged high dose TMX [43–47].

In summary, we did not find evidence of benefit from the addition of a daily dose of 40–100 mg of TMX to the standard adjuvant treatment of glioblastoma multiforme. Although the nonrandomized setting precludes any definite conclusion, we feel that our findings are not promising enough to recommand a phase III study with these doses and combinations. On the other hand, we found some indications that the addition of TMX to BCNU could increase the rate of hematological toxicity and the risk of DVT. Since recent data suggest that higher doses of TMX could be more useful, this toxicity issue should be considered in future trials.

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