

## EFFICACY OF DIFFERENT REGIMENS OF ADJUVANT RADIOCHEMOTHERAPY FOR TREATMENT OF GLIOBLASTOMA

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**Aims and background:** We retrospectively analyzed the impact of different adjuvant chemotherapy regimens in a group of patients treated for glioblastoma compared to patients receiving only postoperative radiotherapy.

**Material and methods:** Eighty-six consecutive patients underwent radiotherapy between January 2000 and December 2003: 52 patients received radiotherapy alone, 17 patients radiochemotherapy with low-dose temozolomide (20 mg/m<sup>2</sup>) + cyclooxygenase-2-inhibitors (200 mg), 6 patients radiochemotherapy with high-dose temozolomide (50 mg/m<sup>2</sup>). Eleven patients, with unfavorable prognostic factors, were treated with imatinib and 55/2.5 Gy.

**Results:** The groups treated with high- and low-dose temozolomide showed the longest overall survival (median, 21 months and 17 months, respectively). Median overall survival was 9 months for radiation alone and 4 months for the imatinib-

treated group. The same positive trend of temozolomide on prolonged overall survival was confirmed when only patients submitted to maximally radical resection or patients with KPS >70 were considered. Differences in progression-free survival were not statistically significant.

**Conclusions:** Patients treated with adjuvant temozolomide either inside or outside of study protocols had survival times similar to other reports or randomized studies. The absence of a significant influence of temozolomide on progression-free survival could depend on the unavoidable drawbacks and biases of retrospective investigations or on the definition of relapse used. The unsatisfactory results of radiotherapy plus imatinib may have been due to a high prevalence of unfavorable prognostic factors in the respective patients. The ongoing controlled trial will further define the efficacy of adjuvant/concomitant imatinib.

**Key words:** chemotherapy, glioblastoma, radiotherapy.

### Introduction

Glioblastoma is the most frequent primary CNS malignancy, and the median survival time after diagnosis is around one year<sup>1</sup>. Chemotherapy recently emerged as an additional therapeutic option<sup>2</sup>.

Temozolomide (TEM; Temodal<sup>TM</sup>, Temodar<sup>TM</sup>; Schering-Plough, Kenilworth, NJ, USA), an oral alkylating agent, has demonstrated antitumor activity as a single agent in the treatment of recurrent and newly diagnosed glioblastoma<sup>3,4</sup>. A randomized prospective trial has demonstrated an advantage in overall survival (OS) after the application of TEM at a dose of 75 mg/m<sup>2</sup> once daily for the duration of radiation therapy (42-49 days), 4 weeks later followed by six cycles of TEM, 150 or 200 mg/m<sup>2</sup> daily for 5 days, every 4 weeks<sup>5</sup>. The incidence of grade 3 and 4 toxicity, however, was relatively high. This led other study groups to perform other dose-finding studies<sup>6</sup>. Nevertheless, for the first time, adjuvant chemotherapy prolonged survival for patients with glioblastoma in a randomized setting.

The continuous low-dose scheduling of TEM in combination with an inhibitor of cyclooxygenase-2 (COX-2) has been suggested as a novel anti-angiogenic approach in patients with glioblastoma, and a clinical

study showed a possible antiangiogenic effect especially in those tumors with a high angiogenic activity<sup>7</sup>.

Unfortunately, in a substantial subset of patients, monotherapy with TEM does not produce a significant response due to expression of the DNA repair enzyme alkylguanine-DNA alkyltransferase<sup>8</sup>. It is therefore as of now unclear what impact adjuvant chemotherapy has in an unselected population treated routinely in a cooperative neurooncology setting with image-guided surgery and modern radiotherapy.

Imatinib (Gleevec<sup>TM</sup>, formerly STI-571; Novartis Pharmaceuticals, East Hanover, NJ, USA), an inhibitor of PDGF receptors alpha and beta, as well as other selected tyrosine kinases (Bcr-Abl, c-KIT, c-fms), has also been investigated in patients suffering from malignant glioma based on the frequently encountered overexpression of both PDGF and PDGFR<sup>9-11</sup>. Furthermore, radiosensitizing effects of imatinib with significant enhancement of cytotoxic effects of ionizing radiation have been demonstrated<sup>12,13</sup>. Here we report preliminary results for patients treated in a pilot phase leading to a clinical protocol with this new agent.

The purpose of the study was the retrospective analysis of the impact of different adjuvant chemotherapeutic regimens in a group of patients treated for glioblastoma

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both within and outside of a clinical study setting, compared to patients receiving only postoperative radiotherapy. The influence of known prognostic factors like patient age, Karnofsky performance status (KPS) and extent of resection was also evaluated. The potential advantages of the different treatment regimens were analyzed with regard to time to tumor progression and survival time.

## Patients and methods

Between January 2000 and December 2003, 86 consecutive patients were treated with postoperative radiotherapy for glioblastoma multiforme at the Department of Radiation Oncology of the Mannheim Medical Center, University of Heidelberg. The diagnosis of glioblastoma was established histologically: 18 patients (21%) underwent tumor biopsy, 68 patients (79%) were submitted to maximally radical resection following craniotomy at the Department of Neurosurgery, Mannheim University Hospital. This group included the  $R_0$ ,  $R_1$  and  $R_x$  situations after surgery. No patient started radiotherapy with an  $R_2$  situation. Demographics and main characteristics of the patients are described in Table 1.

Radiotherapy was started 3-5 weeks after surgery. Twenty-seven percent of the patients underwent hyperfractionated accelerated radiotherapy with 2 x 1.8 to 54 Gy, and 42% were treated with conventional fractionation of 5 x 2.0 to 60 Gy; 13% of the patients received hypofractionated radiotherapy with 4 x 2.5 to 55 Gy. The median dose was 54 Gy due to a large number of hyperfractionated treatments. Seven patients (8%) received less than 45 Gy because of death during the treatment (2 patients) or deteriorating clinical conditions.

Three-dimensional conformal treatment planning was based on contrast enhanced CT imaging after patient positioning with thermoplastic mask immobilization. In

most cases, two or three wedged fields of a linear accelerator (6 MV) were used. Radiotherapy was delivered to the gross tumor volume with a 2- to 3-cm margin to cover the clinical target volume. In case of gross total resection, with no visible tumor in the postsurgical scan, clinical target volume was defined as a volume with a margin of 2-3 cm around the resection cavity.

Additional chemotherapy administered to 34 of the 86 patients consisted of three different regimens. One treatment consisted of TEM (marketed as Temodal in Europe; Schering-Plough) at a dose of 50 mg/day given during radiotherapy, followed by adjuvant TEM (150-200 mg/m<sup>2</sup> for 5 days during each 28-day cycle) as long as there were no hematologic toxic effects or until progression of the tumor. The other regimen (already presented in detail<sup>7</sup>) consisted of low-dose scheduling of TEM (20 mg/m<sup>2</sup>) given in two single doses in combination with an inhibitor of COX-2 (25 mg rofecoxib/VIOXX until November 2003, then changed to 200 mg celecoxib/celebrex) given 5 times daily starting with radiotherapy. The third regimen included imatinib. Patients submitted to this last chemotherapy treatment were submitted to hypofractionated radiotherapy on 4 consecutive days a week with a single dose per fraction of 2.5 Gy up to a total dose of 55 Gy. Chemotherapy with imatinib was performed at a dose of 600 mg on the last three days of a week. The latter two treatment regimens were part of a study protocol (which had been approved by the local institutional review board) or of a pilot study leading to a formal treatment protocol.

Antiemetic prophylaxis with metoclopramide or a 5-hydroxytryptamine antagonist was not administered routinely before the initial doses of concomitant TEM but only in case of symptoms.

*Statistical evaluation.* Survival times and progression free survival (PFS) times were calculated according to the method of Kaplan and Meier. OS as well as PFS were defined from the date of surgery. The results were evaluated according to the treatment group. Univariate analysis of prognostic factors was carried out by comparing total survival times with the logrank test. Multivariate analysis was performed based on the Cox Proportional Hazard model.

*Surveillance and follow-up.* During radiotherapy, patients were seen every week. Within 4-6 weeks of completion of the primary therapy, patients were followed by clinical and neurologic examinations complemented by contrast-enhanced CT or MRI of the brain. In the following period, patients underwent clinical evaluation and radiological restaging every 4-8 weeks. Tumor progression was defined as an unequivocal increase in tumor size after CT or MRI (no specific volume threshold), or the appearance of new lesions

## Results

In all patients, the histology of the brain tumor was glioblastoma multiforme grade IV according to the

**Table 1 - Demographics and characteristics of the patients**

Parameter	
No. of patients	86
Sex	
Male	50
Female	36
Age, years	
Median	62
Range	29-88
Karnofsky performance status (at presentation to RT-Department)	
≥70	62
<70	24
Extent of surgery	
Biopsy	18
Maximally radical resection	68
Dose of radiotherapy	
<45 Gy	7
45-50 Gy	7
50-54 Gy	11
54-57 Gy	23
57-65 Gy	38
Chemotherapy	
Yes	34
No	52

WHO criteria. Median age was 62 years (range, 29-88). Median OS time for the entire group of 86 patients was 13 months and median PFS was 6 months.

Extent of surgery significantly influenced OS and PFS upon univariate analysis. One-year OS was 70% in patients treated with maximally radical resection and 6% after tumor biopsy, with median OS times of 15 months and 4 months ( $P < 0.001$ ) and median PFS of 7 months and 4 months, respectively ( $P = 0.003$ ). Age, dose and KPS significantly influenced OS in univariate analysis.

Fifty-two patients received radiotherapy alone, 17 received combined radiochemotherapy with low-dose TEM and COX-2 inhibitors, 6 received radiochemotherapy with high-dose TEM, and 11 patients received radiotherapy and imatinib. On comparison of all 4 groups, the groups treated with high-dose TEM and low-dose-TEM showed the longest OS (median, 21 and 17 months, respectively). Median OS of 9 months for the radiation alone group and 4 months for the imatinib group were clearly shorter (Figure 1). As regards PFS, with the definition of progression used in this study, no statistically significant difference could be observed (radiotherapy alone, 7 months; low-dose TEM, 6 months; high-dose TEM, 7 months; imatinib, 4 months) ( $P = 0.32$ ).

All patients treated with TEM had undergone maximally radical resection. The quotas of the maximally

radical resection in the other two groups were respectively 75.5% for the radiotherapy alone group and 54.5% for the imatinib group. When only patients submitted to maximally radical resection were considered, and the group treated with radiochemotherapy with TEM was compared with the group treated with radiotherapy alone, the same positive trend in terms of OS was observed (Figure 2). Chemotherapy with TEM gave the same results also when only patients with  $KPS > 70$  or patients treated with a sufficient dose were analyzed (Figure 3).

Multivariate Cox regression analysis evaluated the influence of age, extent of resection, KPS, chemotherapy and total radiation dose on PFS and OS. The total irradiation dose applied was identified as the only independent factor significantly influencing PFS ( $P = 0.006$ ). Age ( $P = 0.006$ ), extent of tumor resection ( $P = 0.003$ ), and total dose applied ( $P < 0.0001$ ) were identified as independent prognostic factors that significantly influenced OS. The influence of the total dose was also significant in a separate analysis for the two groups biopsy *versus* maximally radical resection.

*Relapse.* The median follow-up was 11.7 months. During the observation period, 71 of the 86 patients developed recurrences (50 local relapses; 21 with multicentric recurrence with distant cerebral satellites); 41 of these 71 patients underwent further treatment. Recurrences were treated with re-irradiation and chemothera-

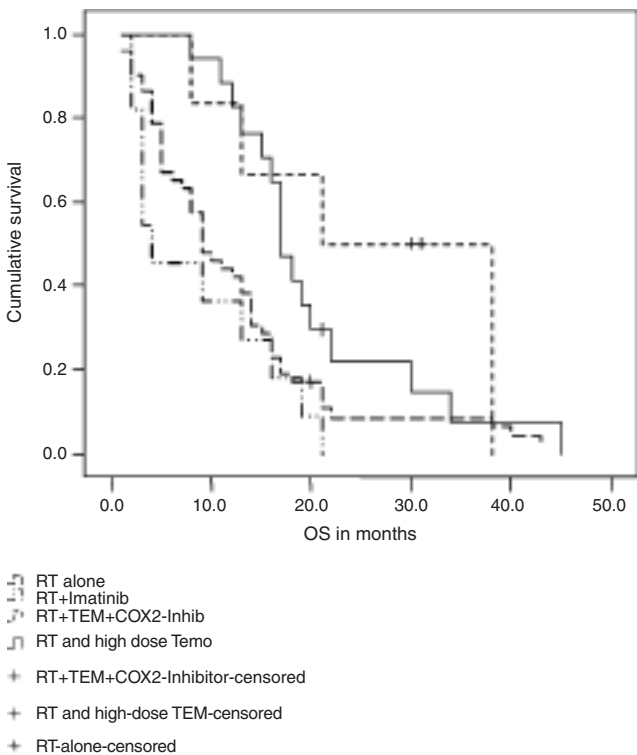


Figure 1 - Overall survival (Kaplan-Meier) in the 4 treatment groups. On comparison of all 4 groups, the groups of patients treated with combined radio-chemotherapy with high-dose temozolomide or low dose Temodal (TEM) showed the longest OS.

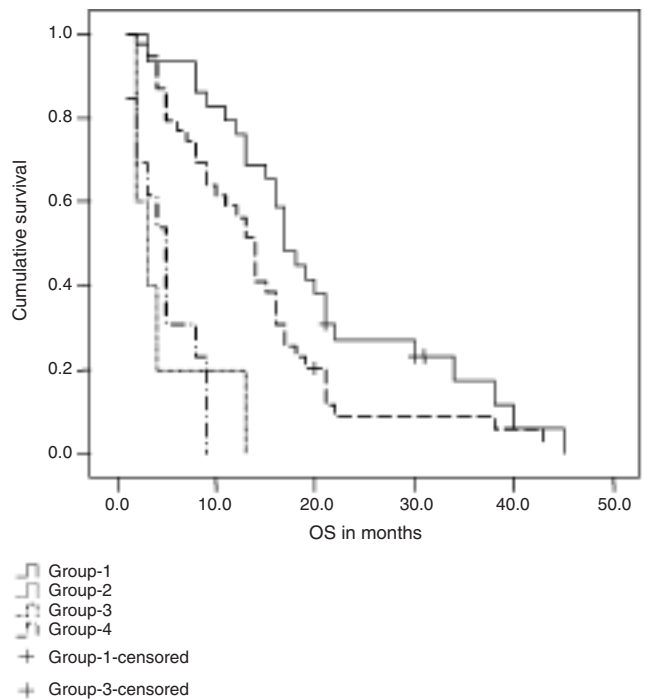


Figure 2 - Overall survival (Kaplan-Meier) curves depending on chemotherapy and type of surgery (1, patients treated with chemotherapy and maximally radical resection; 2, patients treated with chemotherapy and tumor biopsy; 3, patients treated exclusively with radiotherapy after maximally radical resection; 4, patients treated exclusively with radiotherapy after tumor biopsy). Patients with maximally radical resection, adjuvant radiotherapy and adjuvant chemotherapy had the longest median survival.

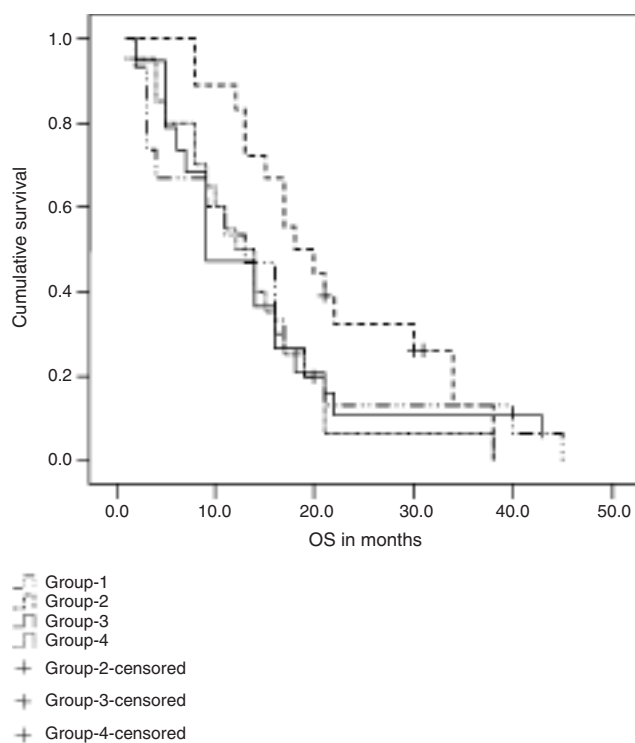


Figure 3 - Survival curves depending on chemotherapy and dose of radiation (1, patients treated with chemotherapy and radiotherapy doses between 50-57 Gy; 2, patients treated with chemotherapy and radiotherapy doses between 57-65 Gy; 3, patients treated exclusively with radiotherapy doses between 50-57 Gy; 4, patients treated exclusively with radiotherapy doses between 57-65 Gy).

py with TEM (13 cases); reoperation, reirradiation and chemotherapy with TEM (6 cases); reoperation and chemotherapy (3 cases); chemotherapy alone with TEM (14 cases); reirradiation alone (3 cases), reoperation and radiation (2 cases). In all cases, TEM was given at the dose of 150-200 mg/m<sup>2</sup> for 5 days every 4 weeks. Thirty patients were not suitable for further treatment. The distribution of the relapses (local *versus* multicentric) is reported in Table 2. Median survival time after relapses was 5.5 months.

**Toxicity.** Toxicity was not analyzed as an end point of our retrospective analysis because not all patients were submitted to routine blood tests during the follow-up. One patient died during radiotherapy because of sepsis, 5 other patients who did not complete the radiation treatment died because of tumor progression.

## Discussion

Different trials have compared radiotherapy alone with radiotherapy plus chemotherapy, given concomitantly with and after radiotherapy, in terms of efficacy and safety. In the randomized, multicentric phase III trial initiated by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC), the addition of TEM to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit. The study demonstrated that the addition of chemotherapy to radiotherapy significantly prolongs survival, with a median increase in survival of 2.5 months (the median survival was 14.6 months with radiotherapy plus TEM and 12.1 months with radiotherapy alone). The 2-year survival rate was 26.5% with radiotherapy plus TEM and 10.4% with radiotherapy alone. The NOA-1 trial confirmed the efficacy in terms of OS of the application of ACNU plus ARA-C or teniposide (VM26) to radiotherapy<sup>14</sup>: median OS and 2-year survival rates of 17.3 months and 25% for ACNU plus VM26, and of 15.7 months and 29% for ACNU plus ARA-C could be achieved for patients with newly diagnosed glioblastoma. Based on these results, the combination of radical surgery, radiotherapy and adjuvant chemotherapy may be the new standard treatment for eligible patients if these data hold up in unselected patients in clinical routine.

Although our study suffers from the unavoidable drawbacks and biases of retrospective clinical investigations, the results of our retrospective study are in accord with the previous results: the median survival period was prolonged in patients treated by combined irradiation and chemotherapy with TEM compared to irradiation alone. In accordance with the literature as well, younger patients, patients submitted to maximally radical resection and patients treated with a sufficient radiotherapy dose had a significantly better outcome in terms of OS.

The favorable outcome of patients treated with TEM could depend on a patient selection bias such as the favorable concomitant submission to complete surgery and the delivering of a dose >54 Gy. However, when in the four treatment groups the subgroups of patients submitted to macroscopically complete tumor resection and the subgroup of patients treated with a total radiation dose >54 Gy were considered, the positive trend of addition of TEM was confirmed.

Table 2 - Distribution of relapses in the different treatment groups

	RT alone	RT + TEM + COX-2 inhibitors	RT + TEM 50 mg/m <sup>2</sup>	RT + imatinib
No relapses	12 (23%)	0	0	3 (27%)
Local relapses	31 (60%)	8 (47%)	6 (100%)	5 (46%)
Multicentric relapses	9 (17%)	9 (53%)	0	3 (27%)

RT, radiotherapy; TEM, temozolomide; COX-2, cyclooxygenase-2.

The unsatisfactory results of the concomitant regimen with radiotherapy + imatinib may result from the fact that most of the patients recruited in this pilot study had unfavorable prognostic factors: 46% of the patient underwent only tumor biopsy and 27% of the patients had a KPS <70. The results of the controlled trial that is underway will further define the efficacy of imatinib in adjuvant and concomitant situations.

The high incidence of distant tumor recurrence especially in the group treated with TEM and COX-2 inhibitors, already confirmed by the pilot study of Tüttenberg *et al.*<sup>7</sup>, may be interpreted as the result of a recently suggested escape mechanism of glioma cells from antiangiogenesis, i.e., an increase in diffuse tumor cell invasion into the adjacent brain following inhibition of tumor vascularization<sup>15,16</sup>.

The reason why chemotherapy as first-line therapy seems to significantly influence OS but not PFS cannot be identified unequivocally. It could be an artifactual effect due to the non-standardized follow-up examination done with different intervals. The definition of progress as an unequivocal increase in the lesion could also be responsible for the absence of difference in terms of PFS. A more precise definition such as an increase of at least 25% according to the modified WHO criteria could theoretically lead to a difference in PFS in the 4 groups. In the previous work published by Tüttenberg *et al.*<sup>7</sup>, the PFS of the low-dose TEM group was reported to be 2 months longer than in our study (8 vs 6 months) but, for the same group of patients, tumor volumetry and the aforementioned cutoff had been applied. This difference in defining progress combined with the interval of 2 months between two follow-up diagnostic examinations explains the different reported value for PFS.

One may further speculate that TEM slows the speed of progression in patients whose tumors are growing

again after an initial phase of tumor regression or stable disease.

The impact of salvage treatment also interferes with the unbiased analysis of the primary treatment. Only randomized trials with clearly defined crossover criteria can prevent that the difference in terms of OS depends exclusively on the concomitant application of TEM and not on a biased treatment of relapses.

In the prospective study of Stupp *et al.*, however, PFS in the two groups (radiotherapy alone *versus* radiotherapy and Temodal) also differed by less than 2 months (median PFS, 5.0 vs 6.9), statistical significance only being reached due to the large number of patients treated<sup>5</sup>. After disease progression, the patients were submitted to different therapy options: 23% of patients in both treatments groups underwent second surgery, 72% of patients in the radiotherapy group and 58% in the radiotherapy + TEM group received further chemotherapy, but the response to salvage therapy/chemotherapy was not recorded as part of the study. This means that the pure effect of TEM as first line chemotherapy on OS was not known precisely even from their study, although the results were very suggestive.

However, in the EORTC study, as well as in our and other studies, even when patients were treated with different therapy regimens for their relapses, the same trend could be observed: patients treated with concomitant TEM have a better OS, and this survival exceeds that reported for glioblastoma until now. If and why a glioblastoma previously treated with TEM is more responsive to relapse therapy should be investigated in further studies.

The results of this retrospective study reproduce the efficacy of adjuvant chemotherapy with TEM as demonstrated in different clinical studies, in both a study- and non-study setting.

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