Abstract. Background: Despite advances in the surgical, radiotherapeutic and chemotherapeutic fields, the outcome for patients with high-grade gliomas remains poor. Our experience of patients treated with and without chemotherapy is reported. 

Materials and Methods: From April 1999 to July 2003, 30 patients with high-grade gliomas were treated: 13 received adjuvant radiotherapy (RT) alone whereas 17 received temozolomide 75 mg/m²/d during the irradiation time and 200 mg/m² daily per 5 consecutive days, every 28 days for three to six cycles, starting 4 weeks after the end of radiotherapy. 

Results: The median follow-up was 12.5 months. The median overall survival (OS) was 15 months. In patients treated with RT plus chemotherapy, no statistical difference was observed between those who had undergone partial surgical resection and those with total resection (p=0.5128). In patients with glioblastoma multiforme (GBM) treated with combined radio-chemotherapy, the median OS was 18 months, while it was 7 months (p=0.0204) in those treated without chemotherapy. 

Multivariate analysis (Cox model) evidenced statistical differences for performance status (p=0.002) and for the type of adjuvant therapy (p=0.006). Conclusion: Radio-chemotherapy plus adjuvant temozolomide seemed to offer the best results in patients not submitted to debulking surgery. The performance status remained the most important prognostic factor. Tolerance to the combined regimen was very good.

Primary brain tumors constitute approximately 2% of all malignant diseases, with an incidence of five to eight per 100,000 persons. More than 17,000 cases are diagnosed annually with approximately 13,000 deaths annually in the United States (1, 2). Grade 3 anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) are the most frequent histologies in adults (3, 4). Surgical resection followed by radiotherapy (RT), with or without adjuvant chemotherapy (5-7), represents the standard management for these patients. Despite advances in the surgical, radiotherapeutic and chemotherapeutic fields, there has been little improvement in outcome with median survival for GBM ranging from 9 to 12 months. The 2-year survival rates are 8-12% for patients with GBM and 38-50% for those with AA (8-11). A meta-analysis suggested an increase of overall survival (OS) of 8.6% at 2 years, and of median survival from 9.4 to 12 months by adding chemotherapy (12). 

Temozolomide is a new alkylating agent with demonstrated activity in primary and recurrent gliomas (13-18). After oral administration, it is rapidly absorbed with high bio-availability (19, 20) and crosses the blood-brain barrier to achieve effective concentrations in the central nervous system (21-23).

The aim of combining temozolomide with radiation was to use an intrinsically active agent (spatial cooperation) that has a different toxicity profile (toxicity independence) and has shown in vitro additive or synergistic activity (radiosensitization) (24, 25). Temozolomide is also thought to inhibit signaling of radiation-triggered migration and invasiveness (26) and to decrease tumor repopulation. 

On the basis of this evidence, and with the aim of improving the outcome in these patients, we started to use concomitant and adjuvant temozolomide in March 2001 and have reviewed all the patients with high-grade gliomas treated in our Institution from April 1999 to July 2003.

Materials and Methods

From April 1999 to July 2003, 30 patients with histologically-proven high-grade gliomas were treated at the radiation oncology operative unit of University of L’Aquila, Italy. Eleven (36.7%) were female and 19 (63.3%) male. The median age was 61 years (range 27-78 years). Twenty-two (73.3%) patients were <70 years old and eight (26.7%) >70 years old. Six patients (20%) were <50 years old. The median performance status (PS) at the time of discovery of the brain lesions was 70 (range 40-90). The median maximum size of the lesion, assessed by imaging, was 4 cm (range 2-7 cm); 18 patients (60%) ≤4 cm and twelve (40%) >4 cm. Before surgery, all patients had undergone a total blood count and brain contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI). All patients underwent...
neurosurgical intervention consisting of partial resection in 15 (50%) and total resection in the other half. These data were confirmed by post-operative imaging. Histologically, 6 (20%) patients had grade III (WHO) astrocytoma and 24 (80%) glioblastoma multiforme (GBM).

The median PS after surgery was 75 (range 50-90). Four to 6 weeks after surgery, the patients received adjuvant radiotherapy (RT). RT was delivered once daily at 2 Gy per fraction, 5 d/wk, for a total of 56-66 Gy (median 66 Gy) with 6-MV photons from the linear accelerator. Ten patients (33.3%) received a total dose ≤60 Gy and 20 (66.7%) received 66 Gy. An adequate immobilization mask was used in all cases. The treatment volumes were determined on the basis of the pre-operative CT or MRI of the brain and generally included the contrast-enhancing lesion with a 3-cm margin up to 50 Gy and with a 2-cm margin for the last 6-16 Gy. Radiotherapy planning always included dedicated CT, three-dimensional reconstruction with treatment planning computation and a beam eye’s view for the choice of the treatment field number, size and shape. Thirteen patients (43.3%), treated from April 1999 to March 2001, received neither concurrent nor adjuvant chemotherapy, whereas 17 patients (56.7%) treated after March 2001 received temozolomide 75 mg/m²/d 1 h before RT (5 d/wk) during all the courses of treatment and 200 mg/m² daily per 5 consecutive days, every 28 days for three to six cycles (median six cycles) starting 4 weeks after the end of radiotherapy. The characteristics of these two groups of patients are summarized in Table I. All patients received anticonvulsants and corticosteroids.

The median PS after RT or concurrent chemo-radiotherapy was 80 (range 40-90). Gadolinium-enhanced MRI, physical examination, haematological and clinical chemistry assessments were performed 4 weeks after the end of RT and then every 3 months; on patients who received adjuvant chemotherapy, haematology and clinical chemistry assessments were performed before each cycle of therapy.

Statistical methods. Toxicity was graded according to the common toxicity criteria (version 2.0). OS was calculated from the time of surgery until death or last follow-up, according to the Kaplan-Meier method and Cox model with SPSS statistical software.
Results

The median follow-up was 12.5 months (range 5-36 months). The median actuarial OS was 15 months (95% C.I.=11-19) for all patients, 1- and 2-year OS were, respectively, 62.6% and 10.3%. Twenty-one patients (70%) died from the disease, four (13.3%) are alive with disease and five (16.7%) are alive without evidence of disease.

Several factors that may influence the OS were analyzed by the Kaplan- Meier method (data are summarized in Table II). Patients treated with adjuvant radiotherapy alone presented a median OS of 13 months (95% C.I.=5-21) and a 1-year OS of 53.8%; in patients who had received combined treatment, the median OS was 15 months (95% C.I.=10-20) and 1-year OS was 69.52% (p=0.7862). Age, maximum tumor size, total dose and histology did not significantly influence the OS. In patients with complete surgical excision, the median OS was 18 months (95% C.I.=15-21), whereas in those with incomplete excision it was 9 months (95% C.I.=3-15) (p=0.0177). The median OS for 21 patients (70%) with post-surgical PS ≥70 was 18 months (95% C.I.=12-24) and for the remaining with PS <70 the median OS was 10 months (95% C.I.=4-16) (p=0.0008). The PS measured before surgery and after RT were also found to be significant prognostic factors (p=0.0018 and 0.0005, respectively).

On analysis of patients treated with radio-chemotherapy, no statistical difference was noticed between those with

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Table II. Univariate analysis for overall survival.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative survival</th>
<th>Log rank test (p)</th>
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<tbody>
<tr>
<td></td>
<td>6 months 12 months 18 months</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>79.2% 57.0% 20.0%</td>
<td>0.0766</td>
</tr>
<tr>
<td>&lt;50</td>
<td>83.3% 83.3% 66.7%</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>75.0% 46.9% 31.2%</td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>86.4% 67.5% 31.7%</td>
<td>0.4947</td>
</tr>
<tr>
<td>Maximum size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 cm</td>
<td>83.3% 72.2% 46.0%</td>
<td>0.0799</td>
</tr>
<tr>
<td>&gt;4 cm</td>
<td>83.3% 46.7% 0.0%</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>83.3% 83.3% 50.0%</td>
<td>0.1036</td>
</tr>
<tr>
<td>GBM</td>
<td>79.2% 57.0% 26.6%</td>
<td></td>
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<tr>
<td>Radiotherapy (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>76.9% 53.8% 26.9%</td>
<td>0.7862</td>
</tr>
<tr>
<td>Plus chemotherapy</td>
<td>88.2% 69.5% 37.1%</td>
<td></td>
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<tr>
<td>Radiotherapy (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>62.5% 18.7% 0.0%</td>
<td>0.0204</td>
</tr>
<tr>
<td>Plus chemotherapy</td>
<td>87.5% 67.5% 40.0%</td>
<td></td>
</tr>
<tr>
<td>Total dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 Gy</td>
<td>80.0% 70% 32.89%</td>
<td>0.8841</td>
</tr>
<tr>
<td>≤60 Gy</td>
<td>90.0% 50.0% 30.0%</td>
<td></td>
</tr>
<tr>
<td>PS after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>90.5% 76.2% 48.9%</td>
<td>0.0008</td>
</tr>
<tr>
<td>&lt;70</td>
<td>66.7% 33.3% 0.0%</td>
<td></td>
</tr>
<tr>
<td>Extent of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial removal</td>
<td>66.7% 40.0% 24.0%</td>
<td>0.0177</td>
</tr>
<tr>
<td>Macroscopic removal</td>
<td>93.3% 86.2% 43.1%</td>
<td></td>
</tr>
</tbody>
</table>

1: All patients.
2: Glioblastoma multiforme patients.
PS: Performance status.
partial surgical resection and those with total resection ($p=0.5128$) (Figure 1). Patients who had received partial resection (8/17 cases) showed a median OS of 13 months (95% C.I.=9-17), whereas patients submitted to total resection (9/17 cases) showed a median OS of 18 months (95% C.I.=10-26). On the contrary, in patients treated with RT alone, a statistical difference was maintained ($p=0.02$); patients with partial resection (7/13 cases) presented a median OS of 7 months (95% C.I.=4-10) and those with complete resection (6/13 cases) a median OS of 18 months (95% C.I.=14-22).

In patients with GBM treated with combined radio-chemotherapy (16/24 cases), the median OS was 18 months (95% C.I.=10-26), while it was 7 months (95% C.I.=3-11) ($p=0.204$) in those treated without chemotherapy (Figure 2). In patients with grade III astrocytoma, only one out of six received the combined schedule (death from disease after 10 months), and five received radiotherapy as the only adjuvant treatment with a median OS of 23 months (95% C.I.=12-34).

Multivariate analysis (Cox model) evidenced statistical differences for PS ($\geq 70$ versus $<70$) ($p=0.002$) and for the type of adjuvant therapy (combined radio-chemotherapy versus radiotherapy alone) ($p=0.006$). No statistical differences were evidenced for total dose ($\leq 60$ Gy versus 66 Gy) ($p=0.053$), histology ($p=0.085$), type of surgical resection (partial versus total resection) ($p=0.124$) or for age ($\geq 50$ versus $<50$ years) ($p=0.130$). The data are summarized in Table III.

Toxicity. All patients presented various grades of infield alopecia. Temozolomide was interrupted during RT in two patients due to grade III thrombocytopenia (both after 5 weeks); two other patients presented with grade I-II thrombocytopenia, which did not require treatment interruptions. Six patients presented with grade I-II neutropenia. No other hematological toxicities were recorded during the combined treatment modality. Patients treated with adjuvant RT did not report any grade of hematological toxicities.

**Discussion**

Post-operative radiotherapy is considered the standard treatment for high-grade gliomas. In four randomized studies (5, 27-29), patients treated with post-operative...
radiotherapy, using a dose ranging from 45 to 60 Gy, presented a median survival ranging from 23 to 47 weeks with a statistically significant difference in terms of OS with respect to those treated with surgery alone. The results of our study confirmed this data, in that patients treated with radiotherapy alone after surgery presented a median OS of 13 months (95% C.I.=5-21).

With the aim of improving these outcomes, many attempts have been made to increase the total irradiation dose or to test non-conventional fractionation. A Medical Research Council (UK) randomized trial compared 60 Gy in 30 fractions to 45 Gy in 20 fractions in 443 patients (30). The 1-year survival rates for the 60 Gy and 45 Gy arms were 39% and 29%, respectively, with statistical significance. Nelson et al. (31) randomized 626 patients to four study arms in a joint study of the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG): 60 Gy to the whole brain, 60 Gy to the whole brain plus a 10 Gy boost to the tumor, 60 Gy and carmustine, 60 Gy and semustine-dacarbazine. No statistically significant differences in survival were reported among the four arms. The median survival for patients treated with 60 Gy was 9.3 months and for those treated with 70 Gy was 8.2 months. In a recent report carried out at the University of Michigan, USA (32), 34 patients with malignant gliomas received a total dose of 90 Gy using a three-dimensional conformal technique. Analysis of failure showed a predominant central pattern in 78% of the patients, with another 13% presenting in-field failures. The treatments were well tolerated, but the median survival was only 11.7 months. In our study, the median and 1-year OS for patients treated with 66 Gy were 14 months (95% C.I.=9-19) and 70%, respectively, whereas those who had received ≤60 Gy, values of 12 months (95% C.I.=4-20) and 50% (p=0.8841) were obtained. Considering patients who had received radiotherapy without chemotherapy, the median and 1-year OS in the first group were 13 months (95% C.I.=5-21) and 57.1% and 8 months (95% C.I.=0-21) and 50% (p=0.6641) in the second group. However, despite these approaches, this disease remains, in the majority of cases, fatal, being characterized by a rapid and devastating clinical course. Thus, the use of chemotherapy concomitant or adjuvant to radiotherapy to increase the therapeutic effects, has not, to date, been conclusively demonstrated to improve outcomes. In fact, the Medical Research Council (MRC) published the results of a randomized study in which 674 patients were treated with surgery plus radiotherapy or additional procarbazine, lomustine and vincristine (33) with no statistical difference in median survival (9.5 vs. 10 months). For patients with AA treated without chemotherapy, the median and 2-year survival were, respectively, 13 months and 37% with an increase of 8 weeks in median and of 5.5% in 2-year survival in those treated with chemotherapy. For GBM patients, the median and 2-year survival rates were 9 months and 8%, respectively, for those treated without chemotherapy, with a 2-week and 1% increase for those who received chemotherapy. In this study, 34% of patients had undergone only biopsy as the sole surgical management. Fine et al. (34) assumed that chemotherapy gave the best results in patients who had received optimal radiotherapy, since these patients should have a reduction in the tumor size and residual disease can be easily inactivated with chemotherapy. On the contrary, the MRC reported that chemotherapy may improve survival in patients with lower doses of radiation, indicating that 45 Gy irradiation plus chemotherapy is similar to 60 Gy alone.

Forty-seven GBM patients were treated, in a phase I RTOG trial, with concomitant RT plus topotecan, with a median survival of 9.7 months (35). Del Rove et al. treated 124 GBM patients with concomitant RT and tirapazamine at 159 µg/m² and 260 µg/m², with the aim of improving the efficacy of radiotherapy to hypoxic areas, and reported median survivals of 10.8 and 9.5 months, respectively (36). Kleinberg et al. (37) obtained a median survival of 12.8 months for patients treated with concomitant RT plus cisplatin and BCNU, results which were not significantly better than sequential chemo-radiotherapy. Beauchesne et al. tested a concomitant-to-sequential use of etoposide and radiotherapy and reported a median survival for patients with GBM of 13.9 months (38).

All the above Authors reported median survivals and survival rates that are not dissimilar to those obtained with radiotherapy alone. However, the recent and more comprehensive meta-analysis and systemic review published by the Glioma Meta-analysis Trialist (GMT) Group (39) reported a small, but clear statistically significant improvement in survival with the use of any adjuvant chemotherapy. The results of this meta-analysis came only from properly randomized trials and included patients who had had appropriate surgery, radiotherapy and chemotherapy. This group reported a 15% relative reduction in the risk of death, an absolute improvement in 1- and 2-year OS of 6% (from 40% to 46%) and 5% (from 15% to 20%), respectively, associated with adjuvant regimes containing chemotherapeutic treatment with respect to radiotherapy alone; the 2-year survival for patients with GBM increased from 9% to 13%, whereas for those with AA it increased from 31% to 37%. No advantage was reported on increasing the total dose over 60 Gy.

Furthermore, the use of temozolomide concomitant and adjuvant to radiotherapy may constitute a novel beneficial approach. Stupp et al. treated 64 GBM patients with a combined schedule similar to ours and reported a median survival of 16 months. In patients submitted to debulking surgery and in those who had not received debulking
surgery, median survivals of 17 and 5 months, respectively, were obtained (40). In our study, for GBM patients treated with combined radio-chemotherapy, a median and 1-year survival rate of 18 months and 67.5%, respectively, was recorded, while for those treated with radiotherapy alone they were 7 months and 37.5%. Patients treated with radio-chemotherapy, who had received partial resection, showed a median OS of 13 months (95% C.I. = 9-17), whereas those submitted to total resection showed a median OS of 18 months (95% C.I. = 10-26), without statistical difference both in univariate and multivariate analyses. These data are encouraging, but should be confirmed with a longer follow-up and with the analysis of a larger number of patients.

Our results confirmed the importance of the PS as a prognostic factor. By analyzing pre-operative, post-operative and post-radiotherapy PS, a statistically significantly better result was obtained in all cases with PS ≥70 (p = 0.0018, p = 0.0008 and p = 0.0005, respectively). In detail, patients with a post-operative PS ≥70 presented median and 1- and 2-year survival rates of 18 months (95% C.I. = 12-24), 76.19% and 15.71%, respectively; whereas in those with post-operative PS <70, the respective values were 10 months (95% C.I. = 4-16), 33.33% and 0%. In multivariate analysis the PS, using the post-operative value, also demonstrated statistical significance (p = 0.006).

On the other hand, elderly patients with a good pre-treatment PS may benefit from conventional treatment (41). In our study, age did not represent a negative prognostic factor, and the median and 1-year survival rates for patients age ≥70 years were 10 months (95% C.I. = 4-16) and 46.9%, respectively, while for those <70 years the rates were 16 months (95% C.I. = 10-22) and 67.5%, respectively, without statistical difference (p = 0.4947). Multivariate analysis also confirmed this data (p = 0.233). Our data confirmed the results of other authors (42, 43), who reported that elderly patients with PS may be treated with the best possible option.

Tolerance to the combined radio-chemotherapy regimen was very good, with no major complications and good compliance. Not late toxicity was recorded, but this may be due to both the low survival rate and the absence of long follow-up for survival.

Conclusion

Radio-chemotherapy plus adjuvant temozolomide seemed to provide the best results in patients not submitted to debulking surgery. The PS remains the most important prognostic factor. Tolerance to the combined regimen was very good. Further improvement of this outcome could probably be achieved in association with other drugs and/or a different schedule of irradiation, such as a stereotactic boost on residual disease.

References

Valeriani et al: Adjuvant Therapy for High-grade Gliomas


