

Analysis of Long-term Survivors of Glioblastoma Multiforme in a Single Institution with Aggressive Local Retreatment Protocol

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Abstract. *Current treatment methods result in survival beyond 2 years in just a minority of adult patients with glioblastoma multiforme (GBM). Our institution has used an aggressive policy of local retreatment, including surgery and radiotherapy, at first relapse. Long-term survival (>2 years) after such an approach was evaluated. Patients and Methods: A retrospective analysis was carried out of all patients with confirmed histological diagnosis of GBM at relapse. Patients with oligodendroglial component or progression from low-grade glioma were not included. Results: Out of the 30 patients managed with aggressive local retreatment, 8 survived for more than 2 years, but no 5-year survivors were observed. All were younger than 60 years, had a good performance status, RPA class III or IV and a long interval to relapse. Those with the longest survival times had also received two different chemotherapy regimens. However, two of the patients were never treated with chemotherapy. Survival from retreatment was 5-17 months. Conclusion: When selecting patients on the basis of the factors associated with long-term survival, the same sequence of surgery, radiotherapy and chemotherapy that should be considered at first diagnosis might provide a moderate survival extension.*

The survival of patients with glioblastoma multiforme (GBM) has improved after the integration of temozolomide into first-line treatment protocols (1, 2). Nevertheless, recent studies have reported that only 11-27% of temozolomide-treated GBM patients survived for 2 or more years (1-7),

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Key Words: Radiotherapy, chemotherapy, neurosurgery, glioblastoma, glioma, retreatment.

except for a small series with highly selected patients (8). An overview of long-term survival reported in the literature is presented in Table I.

Treatment at tumor recurrence varies tremendously (9, 10). Some institutions offer aggressive local retreatment, while others tend to rely on systemically administered agents. Importantly, most types of retreatment are often limited to these patients in good performance status who responded to previous therapy. Given the usually highly individualised treatment sequences in the few long-term survivors, reported series might be difficult to interpret. Our own policy followed a well-defined pathway, including routine administration of maximum local therapy with regard to both surgery and radiation. The retrospective analysis of long-term survival might therefore add information about the usefulness of such an approach.

Patients and Methods

Between 1994 and 2002, the treatment policy for unifocal supratentorial GBM in adults consisted of maximum resection followed by conventional external beam irradiation (30 fractions of 2 Gy) and chemotherapy (ACNU plus teniposide, later replaced by temozolomide). Patients with poor performance status and/or age ≥ 65 years were not offered chemotherapy and most received short-course radiotherapy. The average number of GBM patients per year was 14. The benefit of chemotherapy appeared smaller during that time than now in the temozolomide era. Therefore, not all patients consented to chemotherapy.

At recurrence, all patients except those with very poor performance status were evaluated for repeated resection by a multidisciplinary tumor board. If resection was not recommended, but reirradiation was a feasible option, histological verification of recurrent GBM was obtained by biopsy. Re-irradiation was performed whenever the interval to first-line radiotherapy was ≥ 3 months and the maximum diameter of the lesion was ≤ 4.5 cm. It was also administered to those patients who underwent repeated surgery. Again, patients in very poor performance status were not offered local retreatment. The preferred fractionation regime was 6 fractions of 5 Gy applied by means of stereotactic radiotherapy

Table I. Long-term survival rates in recent clinical trials in glioblastoma patients.

Reference	Number of patients	Median age (years)	Initial Karnofsky performance status (median)	Tumor resection	Chemotherapy after initial diagnosis	2-Year survival rate
Athanassiou <i>et al.</i> (1)	57	Not given	Not given	58%	Temozolomide	16%
Stupp <i>et al.</i> (2)	287	56	Not given	83%	Temozolomide	27%
Kocher <i>et al.</i> (3)	69	52	80%	67%	Temozolomide	24%
Butowski <i>et al.</i> (4)	61	54	90%	84%	Temozolomide plus cis-retinoic acid	20%
Chang <i>et al.</i> (5)	67	51	90%	80%	Temozolomide plus thalidomide	27%
Balana <i>et al.</i> (6)	40	58	80%	63%	Temozolomide plus cisplatin	11%
Herrlinger <i>et al.</i> (8)	31	51	90%	90%	Temozolomide plus lomustine	45%
Fisher <i>et al.</i> (19)	87	Not given	80 or 90%	71%	Topotecan	11%
Souhami <i>et al.</i> (20)	203	56	90%	Not given	Carmustine	20%

Table II. Patient characteristics of long-term survivors.

Patient number	Patient age at first diagnosis	Gender	Initial Karnofsky performance status	Initial RPA class	Chemotherapy after initial diagnosis	Re-resection	Interval to re-irradiation (months)	Chemotherapy at recurrence	Overall survival (months)
1	53	M	70%	IV	ACNU + Teniposide	Yes	24	None	31
2	49	M	80%	IV	none	Yes	20	None	35
3	54	F	100%	IV	none	Yes	34	None	40
4	35	M	100%	III	ACNU + Teniposide	Yes	36	Temozolomide	53
5	59	M	90%	IV	none	Yes	16	Temozolomide	25
6	56	F	80%	IV	ACNU + Teniposide	Biopsy	28	Temozolomide	41
7	33	M	90%	III	ACNU + Teniposide	Biopsy	36	Temozolomide	47
8	36	F	90%	III	Temozolomide	Yes	20	None	25

ACNU: nimustine; RPA: recursive partitioning analysis.

(11). Overall, 30 GBM patients received stereotactic re-irradiation. In temozolomide-naïve patients, the drug was administered after completion of re-irradiation. To compensate for waiting times, few patients started temozolomide during the interval between resection and re-irradiation. A total of 6 cycles were attempted. Some patients also continued to refuse chemotherapy at recurrence.

In cases of further tumor progression after second-line therapy, best supportive care was recommended. Information on the clinical course and survival of all GBM patients who received re-irradiation with or without repeated resection was updated in 2006 and analysed retrospectively. Only cases without an oligodendroglial tumor component and without previous low-grade histology were considered. Long-term survival was defined as survival for more than 2 years from first diagnosis.

Results

All long-term survivors in this series had two corresponding histological diagnoses of GBM. Table II shows the patients treated during the time interval mentioned above whose survival exceeded 2 years (n=8/30, approximately one long-term survivor per year). None of the patients was older than 60 years at first diagnosis and none had a poor performance

status. All belonged to RPA class III or IV (12). Half of the patients had no neurological symptoms at recurrence, just 2 had motor dysfunction and 1 had seizures. Six of 8 patients were eligible for repeated surgical resection and all had a long interval between initial treatment and recurrence. The 3 patients with the longest survival times received 2 chemotherapy regimens, but this group of b also includes 2 patients who never received chemotherapy and survived for 35 and 40 months, respectively. Five-year survival was not observed in this series. Survival after re-irradiation ranged from 5-17 months.

Discussion

All patients in this retrospective analysis had confirmation of their GBM diagnosis at recurrence and had tumors without an oligodendroglial component. Maximum local treatment plus systemic chemotherapy was attempted, yet some patients opted against chemotherapy. The results, which might be limited by the known disadvantages of retrospective evaluations, suggest that long-term survival in the absence of chemotherapy is possible. However, the

patients with the longest survival times had received two different drug regimens. Recent data suggest that one subset of recurrent GBM is highly chemosensitive (13), although current standard diagnostic assessments do not allow for detection of this subset prior to treatment. It has also been reported that such patients have a high rate of *MGMT* hypermethylation in their tumors (7/9 cases in the series by Martinez *et al.* (14)).

Known prognostic factors such as age, performance status and RPA class appear to characterize the long-term survivors in this series. In addition, a long interval from first diagnosis to recurrence was recorded in all patients. The observation of just one long-term survivor per year confirms the results of other groups (15), which reported that patients with an apparently favourable outcome often had a history of low-grade astrocytoma that subsequently dedifferentiated and that, after excluding such cases, true long-term survivors tended to be relatively young and aggressively treated. An additional finding was that intermediate fibrillary elements were more common and small anaplastic elements were less common than in a control population. Kraus *et al.* also reported high rates of reclassification if the "GBM" histology of long-term survivors was reviewed, as well as the presence of oligodendroglial features in 17% (16).

Another group performed tissue analyses on long-term survivors and matched control patients that suggest a better outcome when the tumors have low MIB-1 and DNA topoisomerase II alpha labeling indices (17). Kraus *et al.* used a comparable design to study the influence of the *PTEN*, *TP53* and *CDKN2A* tumor suppressor genes in two groups of patients, but concluded that none of these explained the variations in outcome (18). Considering the fact that many patients managed aggressively at tumor recurrence have disappointing survival and that 5-year survivors continue to be uncommon among those where the histology has been re-evaluated and confirmed, the continued search for genetic and/or epigenetic factors that might allow for better outcome prediction is warranted. In the meantime, patients with a favorable course after first-line treatment, especially those under 60 years of age and with good performance status, should be evaluated at recurrence by a multidisciplinary tumor board for both repeat resection, a second course of radiotherapy and systemic treatment. Their inclusion in prospective clinical trials should strongly be considered.

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Received May 16, 2007
Accepted June 4, 2007