Treatment of Unresectable Glioblastoma Multiforme

CARSTEN NIEDER, ANCA L. GROSU, SABRINA ASTNER and MICHAEL MOLLS

Department of Radiation Oncology, Klinikum rechts der Isar,
Technical University of Munich, 81675 Munich, Germany

Abstract. *Uncertainty exists about the adequate treatment of adult patients with unresectable, primary, biopsy-proven glioblastoma multiforme (GBM), because the different options for this group of patients have not been evaluated in randomized clinical trials to date. Usually, these patients are lumped together in studies of radiotherapy or combined modality treatment with patients who have undergone extensive surgical resection, although they represent an unfavorable subgroup. This fact led us to review the recently published results for combined radio- and chemotherapy and to compare them with historical data. Management with best supportive care after biopsy resulted in a median survival time of 3 months. Median survival in a historical series of radiotherapy was of the order of 6-7 months and 2-year survival was less than 10%. Combined treatment consistently resulted in a 2-year survival rate of 10-18%. However, the median survival in contemporary series is highly variable, still ranging from 5 to 13 months. Even with the same regimen, large differences in outcome were observed (median survival 5 vs. 9.4 months). In a large randomized trial of radiotherapy vs. radiotherapy plus temozolomide, the subgroup with biopsy only did not benefit significantly from combined treatment. With different radio-chemotherapy approaches, the median survival was approximately 5 months in recursive partitioning analysis (RPA) class VI, but 8-14 months in classes IV and V. Thus, careful patient selection is necessary to avoid overtreatment in prognostically unfavorable groups with unresectable GBM. In patients qualifying for lengthy regimens of radio-chemotherapy, prospective randomized trials should study whether simultaneous radio- and chemotherapy is superior to radiotherapy alone and, if so, what are the effects of addition of either upfront chemotherapy or postradiation chemotherapy. Recent data suggest that class prediction models, based on defined molecular profiles, and assessment of MGMT promoter methylation might contribute to improved patient stratification and decision making.*

In diffusely infiltrating high-grade gliomas, combined modality treatment has gained increasing acceptance, at least in prognostically favorable patients. Usually, these tumors arise supratentorially and, occasionally, multifocal disease might be present. The most malignant type, glioblastoma multiforme (GBM), or World Health Organization (WHO) grade IV glioma, tends to occur in 50 to 70-year-old patients and is histologically characterized by its increased cellularity and mitotic activity with additional necrosis or endothelial proliferation (1). The median survival time is limited to approximately 10-15 months. It has long been recognized that survival varies with the extent of surgical resection (2-5). Factors potentially influencing resectability include tumor location, size, multifocal tumor manifestation and the probability of permanent neurological complications. However, certain prognostic factors such as advanced age, severe comorbidity interfering with the ability to undergo anesthesia and surgery, and poor performance status will also impact on decision making. In selected patients, the surgical procedure is limited to stereotactic biopsy. In these cases, further treatment varies from corticosteroids alone or short-course radiotherapy to extended-course radiotherapy and even combined radio- and chemotherapy. The aim of this review was to define the role of such intensive treatment approaches by comparing the results of recently published series with older studies. Randomized trials addressing this issue in patients with biopsy only are not available.

Materials and Methods

This review compared the results of several treatment strategies, based on a systematic literature search by use of Medline (Pub Med by the National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA). Studies published between 2000 and May 2005 were identified. Those dealing with recurrent tumors or with groups of different histological types of gliomas, but lacking a separate analysis of GBM, were excluded. The majority

Correspondence to: Carsten Nieder, Department of Radiation Oncology, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany. Tel: +49 89 4140 4501, Fax: +49 89 4140 4880, e-mail: cnied@hotmail.com

of published papers did not allow extraction of data for the population of interest, *i.e.* adult patients with unresectable, primary, biopsy-proven GBM, because they included a broad spectrum of GBM and anaplastic gliomas where surgery varied from biopsy to extensive resection, and did not report the outcome for each subgroup separately. Examples of such papers include references (6-8). From the remaining 7 studies, prespecified variables were extracted and compared in Table I (9-15).

Results

In patients with GBM unfit for or declining radiotherapy, management with best supportive care after biopsy resulted in a median survival time of 3 months (16). This analysis included 26 patients treated between 1998 and 2003. The median survival in a historical series of radiotherapy was of the order of 6-7 months (17, 18). This is in accordance with the Radiation Therapy Oncology Group (RTOG) data, derived and pooled from 3 prospective randomized trials and published in 1993 (3). The latter analysis included 645 patients with GBM, of whom 17% had biopsy only. Treatment was radiotherapy alone (60 Gy or more) or radiotherapy plus nitrosourea chemotherapy. The tumor size in the biopsy group was 5-10 cm in 61%, <5 cm in 36% and ≥10 cm in 6%. The median survival was 6.6 months, despite relatively favorable prognostic factors (Karnofsky performance status (KPS) 80-100 in 55%, age <60 years in 63%). The 1-year survival rate was 22%. After 2 years, approximately 6% of the patients were alive. The extent of resection was an independent prognostic factor in multivariate analysis. The same holds true for our own institutional experience in 78 patients treated with radiotherapy after biopsy between 1987 and 1996 (19). None of these patients received chemotherapy. Median survival was 6 months. These data might serve as a basis for comparison with the 7 studies published in the last 5 years, which are shown in Table I.

Only one trial, reported by Stupp *et al.*, had a similar unfavorable median survival as the historical data (10). However, this phase II trial was followed by a much larger randomized phase III trial with the same treatment but better outcome in the biopsy-only subgroups (11). That European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) study with 573 patients included 16% with biopsy only, a figure not different from the 17% in the historical RTOG database (3). The median survival was 7.9 months after radiotherapy alone and 9.4 months after radiotherapy plus temozolomide (difference not statistically significant) (11). The reported data unfortunately do not allow for the assessment of potential prognostic factors.

Simon *et al.* reported a prospective phase II trial of radiotherapy, carbogen plus nicotinamide and intraarterial ACNU in 33 patients (9). A historical control group comprised 38 patients treated with radiotherapy plus either BCNU or intraarterial ACNU (Table I). No significant difference in overall survival was observed between the 2 groups. The median survival was 4.6 months for RPA class VI patients and 8-9 months for classes IV and V, respectively. Age and recursive partitioning analysis (RPA) class (20) were determined as prognostic factors. Even better results were reported by Combs *et al.*, who administered radiotherapy and temozolomide (12). However, the number of patients was very small and the prognostic factors can not be extracted from the paper.

Combination chemotherapy with fotemustine/cisplatin/VP-16 before radiotherapy was administered to 33 patients by Frenay *et al.* (15). A maximum of 6 cycles was planned. In case of progression, radiotherapy was to start immediately. All patients completed 2 cycles. However, due to hematological toxicity, 12 patients stopped after 2 cycles. Eight patients completed 4 cycles and 10 received 5-6 cycles. Overall, 36% of the patients had hematological grades III or IV toxicity. The objective response rate was 27% and the median survival 10 months. Nine patients had second-line chemotherapy. Interestingly, this is the only study reporting on second-line treatment, which might also be an important confounding variable when interpreting survival data.

Barrie *et al.* studied 40 patients with newly diagnosed, unresectable GBM (14). They administered up to 4 cycles of BCNU and temozolomide followed by radiotherapy (60 Gy). In case of progression during chemotherapy, radiotherapy was given immediately. Starting 1 month after completion of radiotherapy, up to 4 additional cycles of chemotherapy were administered. Table I shows the demographic data. Multifocal disease was present in 25%. The median tumor size was 12.6 cm^2. The other studies did not report these tumor characteristics. Four cycles of chemotherapy were completed by 60% of the patients, the others discontinuing because of tumor progression. Seventy-eight percent completed radiotherapy. Fourteen patients (35%) received maintenance chemotherapy. The objective response rate to pre-radiation chemotherapy was 42.5%. The median survival was 12.7 months and median progression-free survival (PFS) 7.4 months. All tumors progressed within 2 years. In RPA class V, the median survival was 14 months, while in RPA class VI, it was 5.3 months. The only other statistically significant prognostic factor was age ≤50 years. Six patients (15%) experienced grade IV adverse events, all related to myelosuppression. For all 162 chemotherapy cycles, 32 grade III or IV events were recorded (20%). Temozolomide plus cisplatin was given by Balana *et al.* (13). In the latter trial, 34% objective responses according to McDonald's criteria (21) were noted prior to radiotherapy, and the median time to progression was 4 months in patients with biopsy only. This contrasts to the median overall survival (OS) of more than 12 months.

Table I. *Overview of recent combined modality studies.*

Author	Study type	No.	Median age in years	Median PS	Total dose [Gy]	Median survival	One-year survival	Two-year survival	Chemotherapy
Simon *et al.* 2003 (9)	Single Inst. Phase II	33	57	WHO 1	59.4	8.4 Months	?	12%	ACNU intraarterial plus
		38	56	WHO1	59.4	8.1 Months	?	12%	Carbogen and Nicotinamide Nitrosourea
Stupp *et al.* 2002 (10)	Two-center Phase II	15	?	?	60	5 Months	?	?	Temozolomide[1]
Stupp *et al.* 2005 (11)	Multi-center Phase III	93	? all ≤70	? all WHO 0-2	60 60	7.9 Months 9.4 Months	? ?	? ?	Temozolomide[2] randomized *vs.* radiotherapy alone
Combs *et al.* 2005 (12)	Single Inst. Phase II	17	?	?	60	10 Months	30%	11%	Temozolomide[3]
Balana *et al.* 2004 (13)	Multi-center Phase II	15	? all ≤70	? all ≥70%	60	12.8 Months	54%	10%	Temozolomide[4] and Cisplatin
Barrie *et al.* 2005 (14)	Single Inst. Phase II	40	61	70-80 in 67.5%	60	12.7 Months	54%	15%	Temozolomide[5] and BCNU
Frenay *et al.* 2000 (15)	Single Inst. Phase II	33	58	WHO 0-1 in 49%	60	10 Months	42%	18%	Fotemustine, Cisplatin and VP16

PS: performance status; WHO: World Health Organization; ?: Data can not be extracted from original publication; [1] 75 mg/m^2/day during radiotherapy and 200 mg/m^2/day for 5 days every 4 weeks for 6 cycles; [2] 75 mg/m^2/day during radiotherapy and 150-200 mg/m^2/day for 5 days every 4 weeks for 6 cycles; [3] 50 mg/m^2/day for 5 days per week concomitant to radiotherapy; [4] 200 mg/m^2/day for 5 days every 4 weeks plus cisplatin 100 mg/m^2 on day 1 for 3 cycles before radiotherapy; [5] 110 mg/m^2/day for 5 days every 42 days with BCNU 150 mg/m^2 on day 1.

Unfortunately, prognostic factors and second-line treatment can not be extracted from the paper for the subgroup of patients with biopsy only.

Discussion

Many authors recommend surgical resection as the initial treatment of choice for GBM (5, 22, 23). Besides establishing a tissue diagnosis, resection might lead to rapid improvement of symptoms, *e.g.,* from mass effects, hydrocephalus *etc.*, and reduction of steroid doses. Despite the inability to cure malignant gliomas by surgery, the macroscopic completeness of a "T1 resection" (referring to the removal of all enhancing tumor) is related to survival (4). Historically, early recurrences after resection prompted investigators to study immediate postoperative radiotherapy (2). Today, this postoperative regimen still remains an important and effective way to increase the time to progression, although it does not lead to cure. Many cytotoxic drugs, most often nitrosoureas and other alkylating agents, have been added to surgery and radiotherapy since the 1970's. They were usually administered after completion of local treatment. Two meta-analyses suggested a moderate increase of survival by adding systemic chemotherapy (24, 25). In general, the optimal drug or drug combination is still a matter of debate. Recently, a large and a small randomized trial of different temozolomide schedules in addition to radiotherapy have been published (11, 26). Both trials found significant differences in median OS and PFS for combined treatment. The best dose and treatment duration for temozolomide is yet undefined.

The purpose of the present review was to define the role of intensive combined modality treatment approaches for patients with unresectable GBM. In the absence of randomized trials for this particular group of patients, we compared the results of recently published series with older studies. Of course, one has to be aware of several problems associated with such comparisons. They include changes in the histological classification of GBM and the definition of surgical resectability, as well as implementation of new prognostic models over time, and the likelihood of different definitions of resectability and selection criteria for treatment in different centers. Whether the histological specimen is representative of the complete tumor after

biopsy only is another open question that led us to focus our review on GBM rather than all high-grade gliomas. Potential sources of bias also include the eligibility for chemotherapy, the distribution of prognostic factors, second-line treatment for progressive disease and the reasons for not attempting surgical resection. In fact, most papers did not report the number of patients with multifocal disease, the exact tumor location or the tumor volume.

Biopsy followed by best supportive care resulted in a median survival of 3 months for patients with GBM (16). The radiotherapy series reported 6-7 months (17-19). However, survival after radiotherapy might be shorter in the presence of additional unfavorable prognostic factors (advanced age, reduced PS). In the randomized radiotherapy trial of Roa *et al.*, patients with GBM, age 60 years or older, had a median survival of 5.1 months (60 Gy over 6 weeks) and 5.6 months (40 Gy over 3 weeks), respectively ($p=0.57$) (27). The median KPS was 70%, median age 71 years and 39% had biopsy only. Thus, short-course radiotherapy might be the preferable option for patients with advanced age and intermediate PS. Younger patients in RPA classes IV or V might be the only candidates for combined modality approaches. The objective response rates to upfront chemotherapy, reported by Balana *et al.*, Barrie *et al.* and Frenay *et al.* ranged from 27-42.5% (13-15). Brada *et al.* reported a multicenter phase II study of temozolomide after biopsy, which also included a few patients with anaplastic astrocytoma (AA) (28). Two cycles were planned before radiotherapy. The objective response rate was 20% (162 assessable patients) and 64% remained progression-free prior to commencing radiotherapy. Overall, the median survival was 10 months. This figure compares well with most of the studies shown in Table I and is higher than that reported by the RTOG in 1993 (3). The 2-year survival rates of the studies in Table I (10-18%) are remarkably consistent.

However, the influence of confounding variables on the apparent improvement of outcome over time is hard to estimate. Have we just learned to offer best supportive care to patients with unfavorable features, short-course radiotherapy to the intermediate group and to include the others in phase II trials of combined modality therapy? Several factors seem to support this argument, for example the 2 temozolomide studies by Stupp *et al.* where the same treatment was given, yet survival was very different, *i.e.* 5 *vs.* 9.4 months (10, 11). Thus, different populations with unresectable GBM vary in their survival by a factor of 2. Use of prognostic models, such as RPA classes, for stratification might help to circumvent this problem. Yet, only 2 studies of combined treatment reported such stratified evaluation (9, 14). They also demonstrated an increase in survival from approximately 5 months in RPA class VI to 8-14 months in classes IV and V. Given these

survival data, despite very intense treatment for class VI, it appears reasonable to exclude such patients from future trials of lengthy courses of chemoradiation.

The main prerequisites for successful chemotherapy are sensitivity of the tumor cells to the mechansims of the drug and sufficient drug exposure. The key issues of tumor heterogeneity with primary and acquired resistance, as well as pharmacokinetics, pharmacodynamics and tumor microenvironment, deserve particular attention because of several facts that are specific for CNS tumors. First of all, the intact blood-brain barrier (BBB) prevents access to the brain for several compounds. Even in areas of BBB disturbance, as present, for example, in high-grade gliomas, the effects of contemporary drug treatment are not satisfactory. Many patients with brain tumors are able to metabolize chemotherapy drugs more rapidly than other tumor patients because of concomitant enzyme-inducing medications that are necessary to treat or prevent seizures. Phenytoin, carbamazepine and phenobarbital induce hepatic cytochrome P450 enzymes, resulting in higher maximum-tolerated drug doses (1).

Over the past decade, several genetic alterations have been linked to glial tumor development and progression, as recently reviewed by our group (1). Numerous strategies are currently being investigated to specifically inhibit the epidermal growth factor receptor (EGFR) pathway. Such strategies can also be used for the purpose of radiosensitization of gliomas (29). Further targets include transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). Reports of up to 180 patients with malignant glioma treated with intravenous ^{125}I-labeled anti-EGFR mAb or ^{131}I-labeled anti-tenascin mAb after surgical resection and standard radiation therapy, with or without chemotherapy, were published (30, 31). From the authors' point of view, survival was encouraging (GBM 13.4 months and 18 months, AA 50.9 months). However, unequivocal proof from randomized trials has to be awaited.

Conclusions

In certain prognostic subgroups of patients, the role of chemotherapy is still questionable. A shift from nitrosourea-based regimens to newer drugs has started after the EORTC/NCIC trial in GBM. For patients with unresectable tumors, the best treatment strategy needs to be defined in prospective randomized trials stratified for prognostic class and certain tumor features. Beyond size and number of lesions, recent data suggest a role for *MGMT* promoter methylation (32). A study comparing radiotherapy with combined radio-chemotherapy certainly appears reasonable. Furthermore, it is necessary to study whether the addition of either upfront chemotherapy or postradiation

chemotherapy is truly superior to simultaneous radio- and chemotherapy. Recent data suggest that class prediction models, based on defined molecular profiles, classify diagnostically challenging malignant glioma in a manner that better correlates with the clinical outcome than does standard pathology (33, 34). It might, therefore, be expected that better prognostic models will be available in the future. Molecular studies have identified promising new targets for therapeutic intervention, the efficacy and safety of which are now being studied. The current experience in cancer treatment shows that several targets should be approached and that it is unlikely for a single therapeutic measure to be applicable to all patients. This includes targeting the same signal transduction pathway at different levels with different compounds. Therefore, rational combinations between established treatments and new approaches, aiming, for example, at inhibition of angiogenesis, induction of apoptosis, or inhibition of several signal transduction pathways, might offer the best opportunity to improve the prognosis. Nevertheless, the treatment of malignant glioma remains challenging. Any new treatment modality must face the difficulty of balancing the desirable effects on relatively resistant tumor cells and the potential negative impact on the quality of life in patients with limited life expectancy.

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