Efficacy and toxicity of CyberKnife re-irradiation and “dose dense” temozolomide for recurrent gliomas

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Abstract

Background Stereotactic radiosurgery (SRS) can be a useful adjunct to the treatment of recurrent glioblastoma multiforme (GBM). Its combination with chemotherapy is attractive for the possible radiosensitization effect and cytotoxicity on tumor cells in distant areas. The aim of this study was to evaluate the efficacy and toxicity of CyberKnife SRS alone and combined with a “dose-dense” administration of temozolomide (TMZ) for recurrent GBM.

Methods Between July 2007 and July 2010, 23 patients underwent CyberKnife SRS. In 12 patients irradiation was combined with TMZ at 75 mg/m²/day for 21 days every 28 days. The median prescription dose in this group was 20 Gy (mean 20.7±4 Gy) with a median number of fractions of 2. The median dose for the 11 patients who underwent SRS alone was 20 Gy (mean 19.9±4.4 Gy; p = NS).

Results The median survival was 12 months for patients who underwent SRS/TMZ and 7 months for those who received SRS alone (p<0.01). The 6-month progression-free survival (PFS) of the SRS/TMZ group was 66.7% vs. 18% for those who underwent SRS alone (p=0.03). The median time to progression (TTP) was 7 months for patients who underwent SRS/TMZ and 4 months for those who underwent SRS alone (p=0.01). Corticosteroid dependency was developed by most patients; radionecrosis was evident in one patient (4.3%) receiving TMZ. Grade 3 hematological toxicity was recorded in >40% of patients receiving chemotherapy.

Conclusions The results suggest that Cyberknife re-treatments are relatively safe using selected dose/fraction schemes. The combination with TMZ improved patients’ outcomes with OS and 6-month PFS that favorably compares with alternative treatments, but the incidence of major adverse effects was >40%. Further studies are warranted.

Keywords Glioblastoma multiforme · Recurrent · Stereotactic radiosurgery · CyberKnife · Temozolamide · Toxicity

Abbreviations

EBRT external beam radiotherapy
fSRT fractionated stereotactic radiotherapy
GBM glioblastoma multiforme
Introduction

There is no standard for neurosurgical interventions in patients with recurrent glioblastoma multiforme (GBM). Surgical treatment of focal recurrence may lead to prolonged growth control [2], but can be safely offered only to a small sub-population of patients [1]. Stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (fSRT) and brachytherapy are logical adjuncts of the current state-of-the-art therapy for recurrent GBM because of their ability to deliver high doses of radiation to a focal target. Comparing these options, SRS appears to be the most convenient, offering a fast, non-invasive treatment that can be completed in 1 or few days and is usually well tolerated.

A number of retrospective reports on the use of SRS and fSRT for recurrent GBM have shown promise [6, 8, 10, 15–17, 19, 20, 22, 24, 28, 30, 32, 37, 40, 42], suggesting SRS and fSRT as a treatment option for recurrent GBM, but the main limitation of focal treatments, including radiosurgery, is the inability to address a diffuse disease that in many cases has already developed microscopic lesions far beyond the limits of the appreciable radiological boundaries. The combination of SRS with a chemotherapeutic strategy may foster the control of local disease while maintaining therapeutic activity on distant microscopic tumor areas. Temozolomide (TMZ) is an alkylating agent with activity in primary and recurrent gliomas [5, 26, 34–36]. Preclinical data demonstrated an additive or even synergistic activity of TMZ in combination with radiotherapy. Current evidence suggests that the benefit of the concomitant use of TMZ is gained from its activity as a radiosensitizer, and further data suggest that even low doses have clinically significant activity with lower rates of toxicity [7, 9]. One limitation of the re-treatment is the high risk of radiation-induced complications. Furthermore, the toxicity of re-irradiation might be increased by the combination with TMZ. In this study, we analyzed the safety and efficacy of two treatment modalities for the management of recurrent GBM, CyberKnife SRS alone and combined with a dose-dense TMZ administration schedule (21 of 28-day schedule at a dose of 75 mg/m²/day). Preliminary data are presented here.

Patients and methods

Patient eligibility

Recurrence had to occur at least 6 months after primary treatment, including surgery and chemo-radiotherapy according to the European Organization for Research and Treatment of Cancer (EORTC) 26,981-22,981/CE.3 regimen [34, 35]; multivoxel spectroscopic MRI (mRS) had to show the tumor recurrence vs. pseudo-progression. Tumor volume had to be <30 cc with uni- or bifocal localization on FLAIR images. These and all demographic and laboratory inclusion criteria are listed in Table 1. All patients were required to provide written informed consent.

Treatment

After a 4-week clearance period to allow recovery from toxicities, a chemo-radiotherapic treatment was planned for patients with recurrent GBM. We planned a stereotactic radiosurgery treatment using the frameless, LINAC-based, robotic suite CyberKnife (Accuray Inc., Sunnyvale, CA). The cyberknife treatment was planned and delivered as previously described [11, 12] in single or multiple sessions delivered 24 h apart. The gross tumor volume (GTV) was defined, on the basis of anatomical MRI sequences, as the contrast-enhancing area. A second volume indicated as a planned treatment volume (PTV) was defined on the basis of the limit of the appreciable radiological boundaries. The combination of SRS with a chemotherapeutic strategy may foster the control of local disease while maintaining therapeutic activity on distant microscopic tumor areas. Temozolomide (TMZ) is an alkylating agent with activity in primary and recurrent gliomas [5, 26, 34–36]. Preclinical data demonstrated an additive or even synergistic activity of TMZ in combination with radiotherapy. Current evidence suggests that the benefit of the concomitant use of TMZ is gained from its activity as a radiosensitizer, and further data suggest that even low doses have clinically significant activity with lower rates of toxicity [7, 9]. One limitation of the re-treatment is the high risk of radiation-induced complications. Furthermore, the toxicity of re-irradiation might be increased by the combination with TMZ. In this study, we analyzed the safety and efficacy of two treatment modalities for the management of recurrent GBM, CyberKnife SRS alone and combined with a dose-dense TMZ administration schedule (21 of 28-day schedule at a dose of 75 mg/m²/day). Preliminary data are presented here.

Table 1  Eligibility criteria

| Adult patients | Recurrent GBM | Recurrence at least 6 months after primary treatment | Spectroscopic MRI evidence of recurrence | RPA class III or IV | KPS ≥70 | Age ≤70 | Life expectancy ≥12 weeks | Tumor volume <30 cc | Unifocal or bifocal tumor | Neutrophils ≥1,500/μl | Platelets ≥100,000 | Hemoglobin ≥10 g/dl | Blood urea nitrogen and serum creatinine <1.5-fold normal values | ALT and AST <3-fold normal values | Alkaline phosphatase <2-fold normal values | No increase in corticosteroids administration 72 h before treatment |
of FLAIR, MRSI, and PWI and DWI imaging as the area of suspect tumor diffusion.

According to the planned treatment volume (PTV) the following dose/fractionation schemes were designed (Table 2): (1) 15–16 Gy/single fraction for PTV <10 cc; (2) 20 Gy in two fractions for PTV ranging between 10–20 cc; (3) 24 Gy in three fractions or 25–27.5 Gy in five fractions for PTV >20 cc. The corresponding biological equivalent doses (BED) of the three dose/fraction schemes were 40–43 Gy, using the linear quadratic model and an α/β=10 for glioma cells. A non-isocentric conformal SRS treatment using an inverse planning optimization procedure was designed.

The chemotherapy strategy consisted of the administration of temozolomide using a 21-of-28-day schedule at a dose of 75 mg/m²/day initiated on the day of SRS treatment. We planned a 3-month treatment period followed by new neuroimaging and patient restaging; a second MRI was considered ×3 months later or in case of neurological deterioration. We planned the interruption of chemotherapy in case of neutrophil count <500/µl for 5 days, or platelets <25,000/µl, or if non-hematological toxicity of grade 3 or greater had occurred. Prophylactic anti-emetic therapy with metoclopramide or a 5-HT antagonist was administered in case of neutrophil count <25,000/µl for 5 days, or platelets <25,000/µl for 5 days, or platelets <25,000/µl, or if non-hematological toxicity of grade 3 or greater had occurred. Prophylactic anti-emetic therapy with metoclopramide or a 5-HT antagonist was administered to all patients. No Pneumocystis jirovecii pneumonia prophylaxis was administered.

Assessment of response and safety

Response was assessed according to Macdonald’s criteria [23]. Neurological examination and steroid dose modification were recorded at each cycle. Neuroimaging with gadolinium-enhanced MRI was performed at least every three cycles or if progression was suspected based on neurological symptoms. Complete response was defined as complete disappearance of all detectable tumors as determined by two gadolinium-enhanced MRI scans of the brain performed not less than 4 weeks apart. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Statistical data analysis

Comparison of survival and progression Kaplan-Meier curves between the two groups was performed using the log-rank test. The chi-square test was used to compare the rate of patients surviving at 1 year and the rates of patients progression-free at 6 months. The unpaired t-test with Welch correction was used to compare doses and fractions. Multiple logistic regression analysis was performed to evaluate the role of chemotherapy as independent prognosticator of good outcome. Data analysis was performed with INSTAT, version 3.0, and PRISM, version 4.0 (GRAPH-PAD, San Diego, CA) and MedCalc® v.9.6.4.0 (Marinakerke, Belgium).

Results

Between July 2007 and July 2010, 23 patients (10 female and 13 male; median age: 58±13 years) with recurrent GBM underwent SRS at the CyberKnife center of the University of Messina, Italy. All patients fulfilled inclusion criteria and were offered the concomitant SRS/TMZ treatment as described. Chemotherapy was administered to 12 patients. Eleven patients, in accordance with the treating oncologist, accepted risks connected with SRS, but refused the chemotherapy. The median SRS doses for patients who underwent SRS/TMZ were 20 Gy (mean 20.7±4 Gy) with a median prescription isodose line of 78% (range 75–80%) and a median number of fractions of 2. The median dose for the 11 patients who underwent SRS alone was 20 Gy (mean 19.9±4.4 Gy) at 78% isodose line (range 75–80%). The mean planned treatment volume (PTV) was 13.8±8.3 cc for the subgroup SRS/TMZ and 15.1±8.2 cc for the subgroup SRS alone (p = NS).

For patients who underwent TMZ dose-dense chemotherapy, three received chemotherapy for 3 months, 6 patients received it for 5 months, two patients for 6 months and one patient for 8 months. The causes of discontinuation were tumor progression in 42%, brain edema in 8%, hematological toxicity in 33% and other causes in 18%.

The median overall survival (OS) of patients who underwent SRS/TMZ was 12 months, whereas that of patients who underwent SRS alone was 7 months (p<0.01) (Fig. 1). The 6-month progression-free survival (PFS) of the patients who underwent SRS/TMZ was 66.7%; for patients who underwent SRS alone it was 18% (p=0.03) (Fig. 2). The median time to progression (TTP) was 7 months for patients who underwent SRS/TMZ and 4 months for those who underwent SRS alone (p=0.01). The 1-year survival was 58% in the SRS/TMS group and 9% in the SRS alone group (p=0.03).

Because patients were not randomized, we analyzed the cohort of patients as a whole and performed a logistic regression analysis to evaluate whether the TMZ was an independent variable with respect to OS and TTP. Using median values for binary transformation, TMZ administration proved to be an independent predictor for improved OS (p=0.02) and TTP (p=0.02).

Toxicity

Acute side effects included fatigue, nausea/vomiting, and asthenia in 65% of patients and worsening of pre-existing neurological symptoms in 13%. Corticosteroid dependency,
defined as the onset of neurological deficits and/or cephalagia requiring daily doses of dexamethasone >4 mg for more than 8 weeks, was developed by ten patients who received a combined SRS/TMZ treatment (83%) and by seven patients who received SRS alone (63%; p = NS). Histologically confirmed radionecrosis who required surgery was evident in one patient (4.2%) treated with TMZ. The most common hematological toxicities were leukopenia and thrombocytopenia. Hematological toxicities occurred in 75% of patients who underwent chemotherapy and was ≥ grade 3 in 33% (neutrophil count <500/μl in 2 patients and platelets <25,000/μl in 2 patients). In one case death was directly attributable to the hematological toxicity.

No opportunistic infections occurred. The most common non-hematological adverse events or laboratory abnormalities were nausea/vomiting, asthenia and mild asymptomatic transaminitis. Combined radio and chemotherapeutic toxicity was 42% in the group receiving both treatments.

### Discussion

In this study patients with recurrent GBM underwent SRS and fractionated SRS using defined doses, fractions and volume schemes. The toxicity of re-irradiation with this approach was relatively low, and results, in terms of survival and 6-month PFS, were comparable to those of other salvage treatments, including re-operation. The combination of SRS with dose-dense TMZ administration significantly improved survival outcome, with patients gaining a median OS of 12 months and a 6-month PFS of 66.7%. Nevertheless, this was associated with a relevant rate of adverse effects.

Radiosurgery has been used to treat gliomas, but the publication of a large phase III study by the Radiation Therapy Oncology Group (RTOG) [33] indicated that SRS before external beam radiotherapy (EBRT) and BCNU did not improve survival for newly diagnosed GBM. That
study, however, did not address the role of SRS delivered as a boost or the use of SRS in the treatment of recurrent disease. In fact, several retrospective studies (see ref. [29] for review) have reported that SRS is associated with prolonged survival in patients with recurrent GBM [10, 15, 16, 19, 20, 24], and a recent case control study showed that recurrent GBM patients treated with SRS require fewer surgical procedures and display a slightly longer survival compared to untreated patients [24]. A multicenter study involving treatment facilities spread across the US and Europe has confirmed a potential role for CyberKnife radiosurgery in the treatment of malignant gliomas [39].

Patients who underwent SRS alone in our study had a median survival after treatment of 7 months. This result favorably compares with those of the re-operation, another focal treatment. The OS of re-operated patients can be extrapolated from a limited number of studies. In a randomized trial, patients who underwent re-operation and implantation of BCNU-impregnated polymer or placebo survived for 31 or 23 weeks, respectively [4]. In a smaller study of 24 patients who underwent repeated surgery the survival was 14 weeks [43]. In a study on surgery plus tailored treatment (chemotherapy in 85% of cases), Barker et al. reported a survival of 36 weeks; patients who received similar treatments without surgery survived 23 weeks [2, 13].

One limitation of re-irradiation of recurrent GBM is the high risk of radiation-induced complications. A study by the RTOG evaluated the toxicity of a radiosurgical treatment of previously irradiated malignant glioma escalating the dose to 24 Gy [31]. They demonstrated a good tolerance for small and medium-sized tumors, but unacceptable toxicity for larger lesions [31]. The volume of tumor and the relative volume of irradiated normal brain resulted critical factors also in other series [8, 15]. Re-irradiation of peri-lesional normal brain may easily result in exceeding the cumulative normalized total dose (NTD)>100 Gy, which is considered critical for the development of radionecrosis in the brain [25]. Actually, patients had the primary tumor bed treated conventionally with 60 Gy with a 2 Gy/day schedule, so we calculated a retreatment BED$_{2Gy}$ of 40 Gy according to the linear quadratic model and a $\alpha/\beta$=10 for the tumor. Because normal brain has an $\alpha/\beta$=2, the risk of overcoming the NTD limit is high, and isodose line distribution is critical. For larger tumors, a single fraction of 16 Gy may result in a suboptimal isodose distribution with a large shell of tissue receiving an NTD>100 Gy. For this reason a fractionated treatment was chosen in those patients.

Surgery and radiosurgery share the inability to address a diffuse disease that in most cases has already developed microscopic lesions far beyond the limits of the appreciable radiological boundaries at the time of recurrence. Therefore, the combination of SRS with systemic therapy appears a logical choice. Still, few studies have examined SRS in combination with chemotherapy for recurrent GBM. One prospective study of SRS for recurrent glioma in conjunction with Marimastat found no survival advantage for recurrent GBM [21]. Other studies have shown that the multi-modality treatment is feasible and well tolerated with similar survival times as other treatment modalities [22, 30, 42]. A growing body of evidence suggests that daily TMZ increases the relative dose intensity and may act as a radiosensitizer when co-administered with radiotherapy [14, 18, 38], making a prolonged TMZ administration regimen a rational choice to be combined with SRS.

The 21/28-day schedule, at doses ranging from 75 to 100 mg/m$^2$/day, has been tested in a small number of studies [27, 41]. Brandes et al. [3] investigated the safety
and efficacy of a dose of 75 mg/m²/day in 33 chemotherapy-naive patients with recurrent GBM. The regimen was fairly well tolerated: only 18% of patients developed grade 3 lymphopenia, but it was cumulative, and nearly all patients who received more than nine cycles developed lymphopenia. They reported a 6-month PFS rate of 30%. Our data are in line with these studies, with 33% grade 3 hematological toxicities and a 6-month PFS of 66% in patients that were previously treated with TMZ according to the EORTC sheme [34, 35].

The small number of patients enrolled and the non-randomized design of our study strongly limit the applicability of results. Nevertheless, some conclusions can be drawn. Re-irradiation was tolerated using the dose/fraction scheme we adopted. The treatment was aimed to maintain a BED≥40 Gy and a NTD<100 Gy. Because the normal brain has a lower α/β, which means a possible rapid increase of the NTD, we used a fractionated scheme to reduce the risk of radionecrosis in larger tumors. The combination of this regimen with dose-dense TMZ chemotherapy seemingly allows an impressive improvement of survival in patients that tolerated the treatment, but the risk of severe complications overcame 40% in this group of patients. Prospective randomized trials are needed to draw definitive conclusions.

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Conflicts of interest None.

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