Journal of Clinical Neuroscience 22 (2015) 468–473

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Outcome of salvage treatment for recurrent glioblastoma

Hong Rye Kim [a,1], Kyung Hwan Kim [b,1], Doo-Sik Kong [b], Ho Jun Seol [b], Do-Hyun Nam [b], Do Hoon Lim [c], Jung-Il Lee [b,*]

[a] Department of Neurosurgery, Konyang University Hospital, Konyang University School of Medicine, Daejeon, Republic of Korea
[b] Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Republic of Korea
[c] Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 15 June 2014
Accepted 13 September 2014

Keywords:
Gamma Knife radiosurgery
Glioblastoma
Recurrent
Salvage treatment
Temozolomide

ABSTRACT

Most glioblastoma (GBM) cases recur within a year and almost all cases recur at some point. Standard treatment for recurrent GBM has not yet been established. We investigated the outcome of various salvage treatments for recurrent GBM. Retrospective analysis was undertaken in 144 patients who received salvage treatment at the time of first progression after maximum debulking surgery followed by concomitant chemoradiotherapy and adjuvant temozolomide (TMZ) chemotherapy. The median follow-up period was 18.2 months. We grouped these patients into five groups according to the salvage modalities: Gamma Knife radiosurgery (GKS) group (n = 29), TMZ group (n = 31), GKS+TMZ group (n = 28), reoperation group (n = 38) and "other treatment" group (n = 18). The median time to first progression from initial diagnosis was 8.8 months. The median overall survival (OS) of the five different treatment groups; GKS, TMZ, GKS+TMZ, reoperation, and "other treatment", was 9.2, 5.6, 15.5, 13.2, and 8.0 months, respectively. Median progression-free survival (PFS) was 3.6, 2.3, 6.0, 4.3, and 2.6 months, respectively. Pairwise comparison of OS of the GKS+TMZ group with the other groups showed that the OS of the GKS+TMZ group was significantly better than all others except the reoperation group. Statistically significant prolongation of PFS was observed in the GKS+TMZ group compared with the TMZ group and the "other treatment" group. GKS followed by TMZ salvage treatment was a good prognostic factor for both PFS and OS in multivariate analysis. Retrospectively, GKS+TMZ as a salvage treatment, tended to provide a superior survival benefit at the time of recurrence.

1. Introduction

The survival of patients with newly diagnosed glioblastoma (GBM) has improved modestly since the introduction of temozolomide (TMZ). Stupp et al. reported a standard treatment schedule for GBM composed of concomitant chemoradiotherapy (CCRT) with TMZ followed by six cycles of adjuvant TMZ, which increased the median survival from 12.1 to 14.6 months [1]. Despite advances in imaging, surgical techniques, and first-line treatment, most GBM cases recur within a year and almost all cases recur at some point. GBM is thus, an incurable disease with a dismal prognosis [1], and developing effective salvage treatment at recurrence is essential for prolonging overall survival. However standard treatment for recurrent GBM after first-line treatment has not been established.

TMZ is an alkylating drug with antineoplastic activity even after prior TMZ chemotherapy. The use of TMZ rechallenge has been reported to have substantial survival benefits [2–5]. TMZ has shown good tolerability and clinical efficacy at various doses, even as a salvage therapy, hence it is considered a mainstay therapy for combination with other treatment options [2].

Results from several retrospective analyses have suggested that stereotactic radiosurgery (SRS) is a useful option for recurrent GBM [6–8]. SRS has been considered an alternative to open surgery for surgically inaccessible recurrent lesions. It has superior local tumor control rates to reoperation for small GBM tumors at the time of recurrence [9]. TMZ has potential radio-sensitizing activity in recurrent gliomas, and the advantage of a salvage treatment combining SRS and TMZ chemotherapy has been suggested [10–12].

We investigated the outcome of various salvage treatments for recurrent GBM which had been previously treated with resection and CCRT followed by adjuvant TMZ. We particularly focused on the combination of SRS and subsequent TMZ.

* Corresponding author. Tel.: +82 2 3410 3494; fax: +82 2 3410 0048.
E-mail address: jilee.lee@samsung.com (J.-I. Lee).
[1] These authors have contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.jocn.2014.09.018
0967-5868/

2. Materials and methods

We identified 437 consecutive patients with a histological diagnosis of GBM who were treated at our institute between January 2002 and December 2011. The study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (SMC 2014-02-001) and adhered to the recommendations for biomedical research involving human subjects in the Declaration of Helsinki (1975). The requirement for informed consent was waived, as the study was based on existing clinical data.

Standard first-line treatment was given to 222 patients. We defined standard treatment as maximum debulking surgery (excluding biopsy only) followed by CCRT. CCRT was defined as continuous delivery of 75 mg/m^2 of TMZ for 6 weeks combined with a total of 5000–6000 cGy of external beam radiotherapy (RT) with conventional fractionation, and conventional adjuvant TMZ, 150 mg/m^2 to 200 mg/m^2 given 5 days of each 28 day cycle, for up to six cycles. Patients who did not complete CCRT due to unexpected surgical or medical complications were excluded from this study, whereas those with disease progression after CCRT but before completion of adjuvant TMZ treatment were included in the analysis.

Of the 222 patients with recurrent GBM who underwent standard treatment, 144 patients who received a salvage treatment at the time of first progression were included in this study. The other 78 patients were excluded due to inadequate follow-up data (61 patients) or because they received no further salvage treatment due to poor performance status (17 patients). In total, 81 men and 63 women were included in the study. The median age at initial diagnosis was 51 years (range, 23–87 years). The median follow-up period was 18.2 months (range, 4.4–58.9 months). We grouped these patients into five groups according to the salvage modalities they received. The first group was composed of patients who received Gamma Knife stereotactic radiosurgery (GKS) only; the GKS group (n = 29). The second group was composed of patients who received TMZ chemotherapy only (TMZ group, n = 31). Patients in the TMZ group were given TMZ at either 50 mg/m^2 daily (metronomic dose) or 150–200 mg/m^2 for 5 days per 4 weeks (conventional dose) depending on the clinician's preference. The third group consisted of patients who were treated with a combination of GKS and TMZ, either metronomic or conventional (GKS+TMZ group, n = 28), of which 67.9% received metronomic TMZ chemotherapy. Patients in the fourth group underwent reoperation with or without adjuvant chemotherapy or conventional RT (reoperation group, n = 38). The other patients, who did not belong to any of the previously described four groups, received various salvage treatments, including nitrosourea, procarbazine, vincristine, irinotecan, bevacizumab, intrathecal methotrexate, and re-RT ("other treatment" group, n = 18). The diagram of patient selection is shown in Figure 1.

Individual tumor volume at the time of recurrence was obtained from T1-weighted MRI using the Medtronic StealthStation S7 system (Medtronic Sofamor Danek, Memphis, TN, USA).

All SRS procedures were performed with a Leksell Gamma Knife (Elekta AB, Stockholm, Sweden). All patients were placed in a stereotactic head frame, and high-resolution contrast-enhanced MRI were obtained for treatment planning. Target volume for treatment was defined to cover the enhancing lesion. The treated median tumor volume of the GKS+TMZ group and the GKS group was 9.8 cm^3 (range, 0.6–49 cm^3) and 11 cm^3 (range, 0.5–40 cm^3), respectively. The median prescription dose delivered to the tumor margin for both the GKS+TMZ group and the GKS group was 15 Gy (range, 5–20 and 9–30, respectively).

Follow-up MRI after treatment for recurrent tumor was done every 3 months or at any time when neurological change suggested tumor progression or treatment complication.

The endpoints of the analysis were overall survival (OS), progression-free survival (PFS) and 6 month progression-free survival (6-PFS) from the start of the salvage treatment. OS was defined as the time from the start of salvage treatment to the date of death from any cause, censored at the date of last contact. PFS was defined as the time from the start of the salvage treatment to the date of second progression or death, and censored at the date of last contact. The OS rate and PFS rate were estimated by the Kaplan–Meier method. The OS and PFS for the GKS+TMZ group were compared with each of the other groups using the log-rank test. The OS rate and PFS rate were analyzed with prognostic factors, including sex, age (dichotomized as <65 years or ⩾65 years), Eastern Cooperative Oncology Group (ECOG) score at the first progression (0–1 = good, 2–4 = poor), the extent of resection (total *versus* subtotal), the type of recurrence (in-field or out-of-field) and the interval from diagnosis to the first progression (dichotomized as <9 months or ⩾9 months).

A Kruskal–Wallis test was used to compare tumor volume of the five groups at time of recurrence. Multivariate Cox proportional hazard regression models were used to estimate the hazard ratio (HR) of anticipated prognostic factors at progression. Two-sided p value of <0.05 was considered to be statistically significant for all tests. We used the Statistical Package for the Social Sciences software version 18.0 (SPSS, Chicago, IL, USA).

3. Results

The demographic characteristics of each group are described in Table 1. A good ECOG performance score (0–1) at first progression was found in 89 patients (61.8%) and macroscopic tumor resection was achieved in 83 patients (57.6%). Seventy-eight patients (54.2%) completed over six cycles of adjuvant TMZ chemotherapy. The median period from initial diagnosis to first progression was 8.8 months (range, 1.7–37 months). There were no significant differences in age, sex, performance status at first progression, the extent of surgery, adjuvant TMZ cycles and the time to first progression in the five groups by chi-squared tests.

Recurrence pattern at the first progression were not statistically different in each salvage treatment group, except that in-field recurrence was higher in the reoperation group while out-of-field recurrence or leptomeningeal seeding (n = 8) was more common in the "other treatment" group. The median volume of recurrent tumor in the five treatment groups; GKS, TMZ, GKS+TMZ, reoperation and "other treatment", was 11, 13.7, 9.8, 17.4 and 5.2 cm^3, respectively. There were no statistically significant differences among the five groups by Kruskal–Wallis test (p = 0.053). Progression of the tumor after salvage treatment was confirmed by imaging in 111 patients (77.1%), and 55 (38.2%) received a different second salvage treatment.

3.1. OS and PFS

The median OS, from the date of diagnosis to the date of last follow-up or death, was 18.7 months (95% confidence interval [CI] 15.8–21.5 months) in all 144 patients. The median OS and PFS from the start of salvage treatment were 9.9 months (95% CI 8.5–11.3 months) and 3.9 months (95% CI 3.3–4.5 months), respectively, and the 6-PFS rate was 33.9% (95% CI 29.7–38.1%).

The median OS of the five treatment groups; GKS, TMZ, GKS+TMZ, reoperation and "other treatment", was 9.2, 5.6, 15.5, 13.2 and 8.0 months, respectively. Median PFS was 3.6, 2.3, 6.0, 4.3 and 2.6 months, respectively. Six month PFS rate was 31.5%, 16.4%, 48.8%, 33.2% and 31.6%, respectively. Pairwise comparison of OS of the GKS+TMZ group with other groups indicated that the OS of the GKS+TMZ group was significantly better than all other groups except the reoperation group. PFS was significantly