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Clinical Study

The survival significance of a measurable enhancing lesion after completing standard treatment for newly diagnosed glioblastoma

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ABSTRACT

The goal of this study was to analyze the survival outcome according to the treatment response after completing standard treatment protocol for newly diagnosed glioblastoma (GBM) and to suggest a patient who should be considered for further treatment. After approving by our Institutional Review Board, 57 patients (38 male, 19 female; median age, 52 years; age range, 16–81 years) with newly diagnosed GBM who completed standard treatment protocol were examined retrospectively. According to the treatment response using the RANO criteria, there were 20 patients with complete response (CR), five patients with partial response (PR), 13 patients with stable disease (SD) and 19 patients with progressive disease (PD) after the completion of standard treatment. Patients (PR + SD + PD) with a measurable enhancing lesion were categorized the MEL group (n = 37). We analyzed the difference of survival outcome between CR group and MEL group. The median progression-free survival (PFS) in the CR group was significantly better than that of the MEL group (18.0 months vs. 3.0 months, $p = 0.004$). The median overall survival (OS) was also significantly longer in the CR group (25.0 months vs. 15.0 months, $p = 0.005$). However, there was no significant difference in the survival outcome of the CR group compared with that of the subset of MEL group patients who showed PR or SD. Poor survival outcome was found only in MEL group patients who exhibited progression. Patients with a measurable enhancing lesion showing progression after completion of standard treatment protocol are appropriate candidates for further treatment.

1. Introduction

It has been a decade since concomitant temozolomide (TMZ)-based chemoradiotherapy (CCRT) followed by six cycles of adjuvant TMZ was established as a standard treatment protocol for newly diagnosed glioblastoma (GBM) [1,2]. However, questions about the optimal duration of adjuvant TMZ have been raised [3]. Although the standard treatment protocol uses six cycles of adjuvant TMZ, many clinicians frequently encounter reluctance about stopping TMZ, especially if there is a residual lesion; thus, clinicians are usually willing to consider additional cycles with the expectation of improved outcome. Several studies report improved survival outcomes without increased toxicity as a result of prolonged adjuvant TMZ (i.e., more than six cycles) in patients with newly diagnosed GBM [4–6]. However, the adverse effect of long-term TMZ should be more cautiously examined due to the oncogenic effects of the alkylating agent and myelosuppression [7–10]. The mutagenic potential of high-dose TMZ has been shown in an animal model, and a few patients with TMZ-related leukemia have been reported [11,12]. In addition, administration of prolonged adjuvant TMZ is associated with a substantial economic burden to society [13]. Therefore, prolonged administration of TMZ

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should not be applied to all patients; instead, the subgroups of patients that are likely to benefit should be carefully selected. However, there are little data available to address this issue. Because, most studies report the benefit of prolonged adjuvant TMZ regardless of the treatment response after completing standard treatment protocol [4–6]. Therefore, additional knowledge about the natural survival outcome in patients with a measurable enhancing lesion after standard treatment protocol is required to determine the need for further treatment. In this study, we analyzed the survival outcome of patients with newly diagnosed GBM according to the treatment response after patients completed the standard treatment protocol. Further, we attempted to suggest the patient subgroups that should be considered for further treatment.

2. Materials and methods

2.1. Patients selection

Clinical data were retrospectively reviewed for patients with newly diagnosed GBM at the Seoul National University Hospital from January 2008 through December 2011. The study was approved by the Institutional Review Board. The outline of the patient selection process is described in Figure 1. Among 192 patients, 144 patients were treated with the standard treatment protocol after surgical resection or biopsy. All patients were managed based on the response assessment in neuro-oncology (RANO) criteria for high-grade gliomas during standard treatment [14]. Among those patients treated with the standard protocol, completion of the protocol was achieved in 66 (45.8%); no further treatment was provided to these patients. 78 (54.2%) patients discontinued the standard treatment protocol for salvage therapies or supportive care because of disease progression. Fifty-seven patients were enrolled and analyzed; nine patients were excluded due to incomplete radiological data. The median age at the time of pathological diagnosis was 52 years (range, 16–81); 38 patients were male, and 19 patients were female. After surgical resection or biopsy, the median follow-up was 26 months with a range of 11–64 months.

2.2. Analysis of treatment response

In the present study, treatment responses were evaluated at four time points in each enrolled patient considering clinical status and use of corticosteroids as well as the findings of MRI, based on RANO criteria. The time points were as follows: after surgery (within 48 h), after completion of CCRT (within 1 month), during adjuvant TMZ (within 3 weeks after three cycles), and after completion of adjuvant TMZ (within 1 month after six cycles). The MRI sequences for evaluation included fast/turbo spin-echo T2-weighted (T2W) images, fluid-attenuated inversion-recovery (FLAIR) images, diffusion-weighted imaging (DWI) and subsequent contrast-enhanced spin-echo T1-weighted (T1W) images in all enrolled patients. The evaluation of treatment response was conducted and double-checked by a neurosurgeon and neuroradiologist who were not involved in the management of enrolled patients in a blinded fashion. We defined two main groups contingent on the existence of a measurable enhancing lesion on MRI performed after completion of six cycles of adjuvant TMZ. A measurable enhancing lesion was defined according to RANO criteria, bidimensionally contrast-enhancing lesions with clearly defined margins on MRI and two perpendicular diameters of at least 10 mm on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip [14]. One group (CR group) consisted of patients who achieved complete response (CR) after completion of six cycles of adjuvant TMZ (n = 20). The other group (MEL group) consisted of all other patients who had a measurable enhancing lesion on MRI after completion of six cycles of adjuvant TMZ (n = 37). Patient characteristics and clinical data are summarized in Table 1. The final treatment response of the MEL group after completion of six cycles of adjuvant TMZ included five patients with partial responses (PR), 13 with stable disease (SD), and 19 with progressive disease (PD). Of all patients, there were 15 patients (26%) with pseudoprogression finding during standard treatment. Pseudoprogression was defined as the contrast enhancing lesion that eventually stabilizes or shrinks on the follow-up MRI, except for new enhancing lesion beyond the radiation field of 80% isodose line [14].

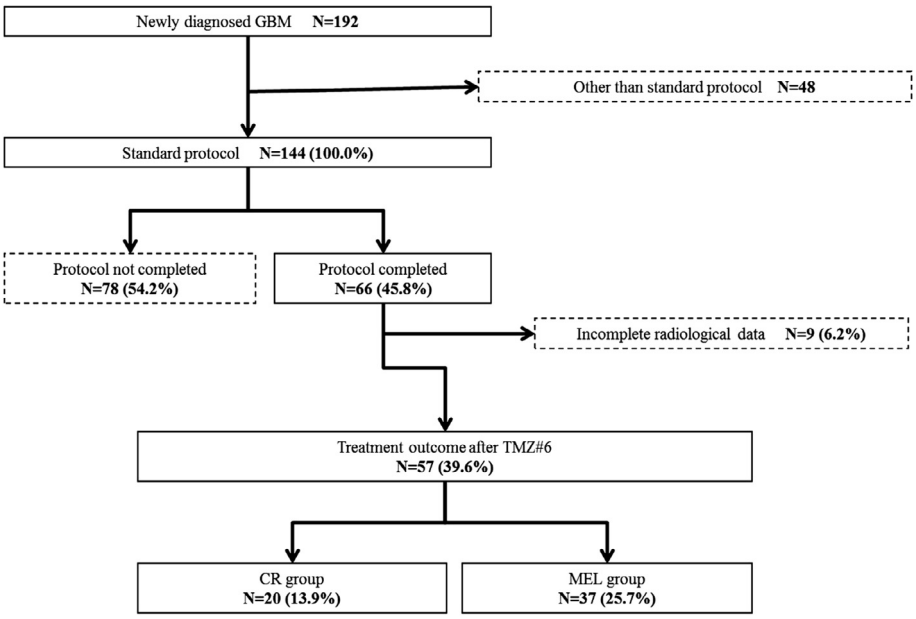

Fig. 1. Selection of patients for the study design. CR = complete response, GBM = glioblastoma multiforme, MEL = measurable enhancing lesion, TMZ = temozolomide.