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Original Research Article

Benefits afforded by combined temozolomide, radiation and stem cell strategy for glioma therapy

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Abstract

Purpose: *To compare the efficacy of temozolomide, radiation and stem cell therapy in glioma management.*
Methods: *A total of 112 patients with glioblastoma were divided into four groups, each of 28 patients. Group I received daily temozolomide at 150 mg/m^2; Group II radiotherapy of 30.0 Gy; Group III mesenchymal stem cells only; and Group IV all three treatments (temozolomide 100 mg/m^2 + 30.0 Gy of radiotherapy + two infusions of mesenchymal stem cells, weekly for 3 weeks. All patients were assessed 1, 6, and 12 months following the conclusion of treatment.*
Results: *Of Group I patients, the maximum improvement in tumor diameter was 58 % but only 28 % ultimately survived. Of Group II patients, the maximum improvement was 49 % but, again, only 28 % survived (p = 0.06 for both groups). Of Group III patients, the maximum improvement was 71 % and 40 % survived. Of Group IV patients, who received all three treatments, the maximum improvement was 80 %. The survival rate was 60 %.*
Conclusion: *Stem cells improved patient outcomes and may be a useful alternative therapy for glioma.*

Keywords: *Glioma therapy, Temozolomide, Stem cells, Prognosis, Radiotherapy*

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INTRODUCTION

Glioblastoma is one of the commonest brain tumors, constituting 50–55 % of all such tumors [1]. Prognosis is poor for several reasons, of which one is recurrence [2]. Other factors include the development of resistance to chemotherapy and radiotherapy, and advanced patient age. Radiotherapy has been the principal postoperative therapy for many decades, but is not fully effective [3]. The levels of molecular markers of glioma progression are higher in elderly patients than in younger adults [4-6]. Temozolomide has been prescribed to both glioma outpatients and inpatients to improve survival and the quality of life, as has radiotherapy. Both treatment modalities increase survival [7,8]. Temozolomide (an alkylating agent) has good oral bioavailability and is well tolerated, so it is widely used to treat glioblastoma [9,10].

Radiotherapy is one of the best supportive care options after surgery [11]. Radiotherapy is well tolerated by many patients; however, toxicities do develop. Some patients improve after treatment [12]. The translational therapies applied over the past 50 years do not cure glioma, but do improve the survival rate. In recent years, a number of innovative therapies have been developed.

Bone marrow-derived stem cells find many clinical applications; the cells are easy to harvest [13]. Clinically, human mesenchymal stem cells

are most often used because they are easily isolated and cultured and can be genetically modified.

In the present study, we compare temozolomide, radiotherapy, and stem cell therapy in terms of effectiveness. Self-renewing agents such as stem cells will be important components of future therapies.

METHODS

We recruited a total of 112 patients with glioblastoma treated in the Department of Neurosurgery, Shanghai Tongji Hospital, Shanghai, China, from January 2014 to April 2016. The study complied with National Institutes of Health guidelines [14] and was approved by the Institutional Ethics Board of the hospital (approval no. STHR 748-19/14). The inclusion criteria were newly diagnosed, pathologically confirmed glioma and age > 50 years. We enrolled both males and females. We excluded patients who were already receiving anticancer treatment and those younger than 50 years of age. Demographic details were collected from hospital records. Clinically, all patients had grade IV astrocytomas, as defined by the World Health Organization (WHO). All patients underwent baseline assessment including a total blood count and physical examination. Weight, height, neurological status, and lifestyle factors were obtained from hospital records or with the aid of a questionnaire.

Patients were divided into four groups, each including 28 of them. Group I consisted of 16 male and 12 female patients aged 55–68 years. They received only temozolomide (150 mg/m^2 for 4 of 25 days; eight cycles). Group II consisted of 14 male and 14 female patients aged 54–66 years. They received only radiotherapy (30.0 Gy for 2 days each week for 4 weeks). Group III consisted of 18 male and 10 female patients aged 59–64 years. They received only bone marrow mesenchymal stem cells, directly injected into the tumor (two injections weekly for 4 weeks; eight doses in all). Group IV consisted of 12 male and 16 female patients aged 50–70 years. They received all three treatments (temozolomide 100 mg/m^2 for 4 of every 25 days [8 cycles]; 30.0 Gy of radiotherapy in fractions of 3.7 Gy for 2 days each week for 4 weeks [8 fractions]; and two doses of mesenchymal stem cells weekly for 3 weeks). All patients were assessed 1, 6, and 12 months after the commencement of treatment. Blood counts were checked every month, especially in patients receiving temozolomide. All side effects were graded using the WHO system [15] and were treated when possible. Otherwise, the glioma treatment was suspended until the side effects subsided.

Statistical analysis

Survival difference between groups was considered significant at $p < 0.01$. Overall survivals were compared using the Kaplan-Meier method. Improvements in the various groups were compared. All statistical analyses were performed with the aid of SPSS software, version 21.0.

RESULTS

Of the 112 glioma patients, 60 (53.6 %) were male and 52 (46.4 %) female, and the mean age was 56 ± 5.8 years. Study data were analyzed every 3 months in terms of prognosis (Figure 1).

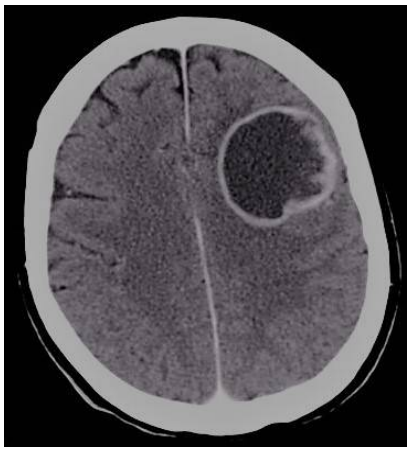

Figure 1: A computed tomography (CT) scan of a patient taken prior to commencement of therapy

Group I patients had a mean weight of 54 ± 5.4 kg and a mean height of 162 ± 3.7 cm (Table 1). Of the 28 patients, 4 (14.3 %) discontinued treatment because of poor prognosis. Fourteen (50 %) patients underwent a second course of treatment. Six (21.4 %) patients improved by a maximum of 58 % (Table 2). The survival rate was only 28%. Three (10.7 %) patients died from disease progression. Three (10.7 %) developed nausea and vomiting; treatment was stopped for 1 week to deal with these problems, and then resumed. Two (7.1 %) patients developed neutropenia and one (3.6 %) an intracranial hemorrhage (Table 3).

In Group II (radiotherapy), the mean patient age was 59 ± 5.9 years, the mean weight was 56 ± 2.8 kg, and the mean height was 154 ± 3.4 cm. The maximum improvement was 49 % (Table 2). Survival was poorer than that of patients who received only temozolomide. Of the 28 patients,

Table 1: Baseline patient characteristics

Parameter	Group I	Group II	Group III	Group IV
Sex				
Male	16 (57.1%)	14 (50%)	18 (64.3%)	12 (42.9%)
Female	12 (42.9%)	14 (50%)	10 (35.7%)	16 (57.1%)
Mean age (years)	60±4.8	59±5.9	60±4.2	64±3.3
Height (cm)	162±3.7	154±3.4 cm	156±5.2	149±4.4
Weight (kg)	54±5.4	56±2.8 kg	60±3.6	63±4.7
Type of treatment	Temozolomide	Radiotherapy	Stem cell therapy	Temozolomide, radiotherapy, stem cell therapy
Dose	150 mg/m^2	30.0 Gy	Two doses on each of 2 days	100 mg/m^2 30.0 Gy Two doses on each of 2 days
Duration of therapy	8 months	4 months	6 months	1 year

Table 2: Progression rates (%)

Group	1 month	6 months	12 months	Survival rate
I	19	37	58	28
II	21	34	49	28
III	30	54	71	40
IV	38	62	80	60

Table 3: Side effects (N, %) in all groups

Side effect	Group I	Group II	Group III	Group IV
Nausea	3 (10.7%)	2 (7.1%)	2 (7.1%)	-
Vomiting	3 (10.7%)	2 (7.1%)	2 (7.1%)	-
Fever	-	-	-	2 (7.1%)
Neutropenia	2 (7.1%)	-	-	2 (7.1%)
Fatigue	-	1 (3.6%)	-	-
Intracranial hemorrhage	1 (3.6%)	-	-	-
Seizures	-	1 (3.6%)	-	-
Thromboembolic disease	-	2 (7.1%)	-	-
Hematological toxicities	-	2 (7.1%)	-	-

22 (78.6 %) completed radiation therapy on schedule. The ultimate survival rate of 28 % was similar to that of patients who received temozolomide only.

The temozolomide and radiotherapy treatments did not differ significantly, and no gender-specific effect was evident. However, the between-group survival time differed ($p < 0.06$). Six (21.4 %) patients developed side effects: one (3.6 %) seizures, two (7.1 %) thromboembolic disease, one (3.6 %) fatigue, and two (7.1 %) hematological toxicities with nausea and vomiting (Table 3).

Group III patients were of mean age 60 ± 4.2 years, mean weight 60 ± 3.6 kg, and mean height 156 ± 5.2 cm (Table 1). They received bone marrow stem cells. The maximum improvement was 71 % and 40 % survived; this rate was better than those of Groups I and II (Table 2). Only two (7.1 %) patients developed side effects (nausea and vomiting). No patient died during the course of the study (Table 3).

Group IV patients were of mean age 64 ± 3.3 years, mean weight 63 ± 3.7 kg, and mean height 149 ± 4.4 cm (Table 1). These patients received all three treatments. The temozolomide doses were 100 mg/m^2 on each of 4 days (eight cycles) and the radiotherapy was identical to that received by Group II patients. The stem cell doses were identical to those of Group III. The maximum improvement was 80 %, thus better than that of the other three groups (Table 2).

Two (7.1 %) patients developed neutropenia and fever. The survival rate was 60 %, which was better than those of the other three groups (Table 3). CT scans showed significant improvement in most patients (Figure 2).

A questionnaire was used to evaluate quality of life after completion of treatment. Group III and

IV patients reported better quality of life than patients in Groups I and II.

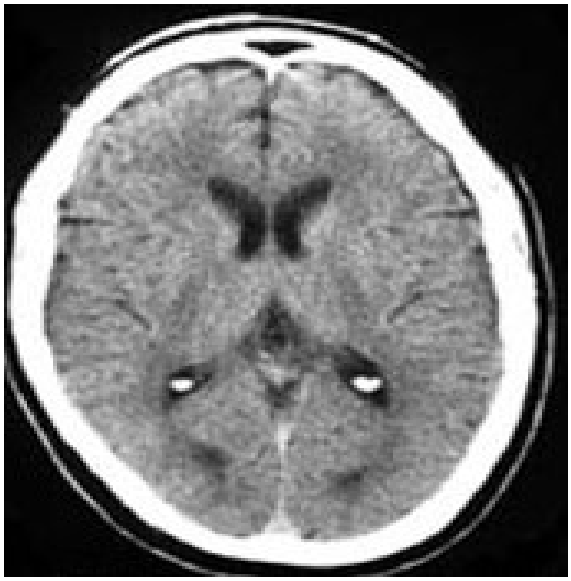

Figure 2: CT scan taken after treatment with mesenchymal stem cells

DISCUSSION

Tumor numbers in the elderly have increased dramatically in recent times. Many studies have described primary brain tumors in those aged ≥ 60 years of age [16]. Clinicians face major challenges when treating gliomas in the elderly. Older age adversely affects the survival rate [17] and many other factors are also in play. Less toxic alternatives to radiotherapy and temozolomide are required [18].

We found that patients given mesenchymal stem cells, alone or in combination with other treatments, had fewer side effects, a better prognosis, and improved more than Group I and II patients (who received temozolomide and radiotherapy, respectively). Some patients could not tolerate the scheduled radiotherapy; this reduced the survival rate and worsened the prognosis [19].

We gave 30.0 Gy of radiotherapy, which was lower than that of the NOA-08 trial; in this latter trial, 60.0 Gy was delivered in fractions of 1.8 – 2.0 Gy. In this previous study, the survival time was 9.6 months, whereas it was 1 year in the present study. This difference may be attributable to geographical variation, patients' living conditions, and/or patient age [19].

The adverse effects that we encountered were similar to those of other studies. The maximum improvement afforded by temozolomide was 58 %, similar to that of other studies in which temozolomide significantly improved survival and the quality of life.

Gliomas are highly infiltrative and develop resistance to conventional therapies [20]. Mesenchymal stem cells from bone marrow afforded a maximum of 71 % improvement, which was better than that of conventional therapies. When stem cell therapy was combined with other therapies, survival and the quality of life improved to 80 %, showing that the stem cells were effective [21].

The results are in line with those of previous reports, highlighting the need for new alternative therapies to improve the survival rate of glioma patients.

CONCLUSION

More research is required to obtain a deeper understanding of the utility of alternative therapies such as stem cells to improve the outcomes of glioblastoma patients.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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