A Phase II study of anti–epidermal growth factor receptor radioimmunotherapy in the treatment of glioblastoma multiforme

Clinical article

LINNA LI, M.D.,¹ TONY S. QUANG, M.D.,² ED J. GRACELY, PH.D.,³ JI H. KIM, M.D.,⁴ JACQUELINE G. ENRICH, PH.D.,⁵ THEODORE E. YAEGER, M.D.,⁶ JOSEPH M. JENRETTE, M.D.,⁷ STEVEN C. COHEN, M.D.,⁸ PERRY BLACK, M.D., C.M.,⁹ AND LUTHER W. BRADY, M.D.⁵

¹Department of Radiation Oncology, Fox Chase Cancer Center; Departments of ²Epidemiology and Biostatistics, ³Radiation Oncology, and ⁴Surgery (Neurosurgery), Drexel University College of Medicine; ⁵Department of Hematology and Oncology, Bryn Mawr Hospital, Philadelphia, Pennsylvania; ⁶Department of Radiation Oncology, VA Puget Sound Health Care System/University of Washington, Seattle, Washington; ⁷Department of Radiation Oncology, City of Hope, Duarte, California; ⁸Department of Radiation Oncology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and ⁹Department of Radiation Oncology, Medical University of South Carolina, Charleston, South Carolina

Object. This single-institution Phase II study tests the efficacy of adjuvant radioimmunotherapy with ¹²⁵I-labeled anti–epidermal growth factor receptor 425 murine monoclonal antibody (¹²⁵I-mAb 425) in patients with newly diagnosed glioblastoma multiforme (GBM).

Methods. A total of 192 patients with GBM were treated with ¹²⁵I-mAb 425 over a course of 3 weekly intravenous injections of 1.8 GBq following surgery and radiation therapy. The primary end point was overall survival, and the secondary end point was toxicity. Additional subgroup analyses were performed comparing treatment with ¹²⁵I-mAb 425 (RIT, 132 patients), ¹²⁵I-mAb 425 and temozolomide (TMZ+RIT, 60 patients), and a historical control group (CTL, 81 patients).

Results. The median age was 53 years (range 19–78 years), and the median Karnofsky Performance Scale score was 80 (range 60–100). The percentage of patients who underwent debulking surgery was 77.6% and that of those receiving temozolomide was 31.3%. The overall median survival was 15.7 months (95% CI 13.6–17.8 months). The 1- and 2-year survivals were 62.5 and 25.5%, respectively. For subgroups RIT and TMZ+RIT, the median survivals were 14.5 and 20.2 months, respectively. No Grade 3 or 4 toxicity was seen with the administration of ¹²⁵I-mAb 425. The CTL patients lacked Karnofsky Performance Scale scores, had poorer survival, were older, and were less likely to receive radiation therapy. On multivariate analysis, the hazard ratios for RIT versus CTL, TMZ+RIT versus CTL, and TMZ+RIT versus RIT were 0.49 (p < 0.001), 0.30 (p < 0.001), and 0.62 (p = 0.008), respectively.

Conclusions. In this large Phase II study of 192 patients with GBM treated with anti–epidermal growth factor receptor ¹²⁵I-mAb 425 radioimmunotherapy, survival was 15.7 months, and treatment was safe and well tolerated.

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Key Words • radioimmunotherapy • glioblastoma multiforme • temozolomide • ¹²⁵I-iodine-labeled monoclonal antibody 425 • anti–epidermal growth factor receptor

Glioblastoma multiforme is the most common and aggressive adult primary tumor of the CNS. The American Cancer Society estimates that there were 12,740 deaths due to CNS tumors in 2008, with GBM accounting for more than 70% of the deaths. Despite aggressive multimodality treatment, the infiltrative nature of GBM renders poor local control and rapid disease progression. Therefore, novel treatments are necessary. The EGFR has been extensively studied as a marker and potential target for high-grade gliomas, it is highly expressed in up to 60–90% in high-grade gliomas. The 425 anti-EGFR antibody (mAb 425) is an IgG2a isotype developed from mice immunized with...
A-431 epidermoid carcinoma cells. In vivo studies in nude rats with stereotactically implanted human glioma cells show a 10–15-fold localization of mAb 425 to high-grade glioma when compared with the contralateral normal brain tissue. In patients with primary gliomas, PET CT scanning with 111indium-labeled mAb 425 shows 90% sensitivity, 60% specificity, and 90% accuracy to the tumor. When binding to the tumor, mAb 425 has anticarcinogenic effects mediated by direct cell growth inhibition, complement-dependent cytotoxicity, and activation of the humoral response. Labeling mAb 425 with radioactive 125I offers synergistic tumor killing through radiation-mediated DNA damage. Initial clinical studies have shown survival benefits of adjuvant 125I-425 mAb in patients in whom GBM has been diagnosed.

For the past 20 years, the standard treatment for patients with GBM consisted of resection followed by radiation therapy with or without nitrosourea-based chemotherapy. In 2005, a landmark trial by Stupp et al. showed that the addition of temozolomide to radiation therapy confers a survival benefit with a reported median survival of 14.6 months. In patients with MGMT promoter methylation who were treated with temozolomide, the median survival was 21.7 months. Temozolomide became part of the standard for treatment of patients with GBM. We now report the updates of our Phase II study in which we investigated the efficacy and safety of adjuvant treatment with 125I-425 mAb in patients with newly diagnosed GBMs. Subgroup analysis was performed in patients who received temozolomide treatment. These results were also compared with our historical institutional database of patients who did not enter into the study. While such analysis does not have the statistical validity of a randomized control arm, the rationale for comparison of the Phase II results with the historical control group is 2-fold. First, such comparisons provide insight regarding the magnitude of patient selection bias. Second, if such biases are reasonably accounted for, this comparison may provide an estimate of the benefits of treatment.

Methods

Study Design

In 1987, a Phase II single institution prospective study (NCT00589706) was designed to assess the efficacy of radioimmunotherapy with anti-EGFR 125I-425 mAb in patients in whom high-grade gliomas were diagnosed following surgery and radiation therapy. The trial was found to be efficacious and promising with minimal side effects during interim analysis. The study remained open for over 20 years because the investigators were ethically compelled to provide patients access to treatment until a Phase III trial became available. This paper reports the 20-year outcomes of patients in whom a GBM was diagnosed. Patients were prospectively evaluated and observed. Considering the short expected survival in this patient population, the primary end point was survival, and the secondary end point was toxicity. Data regarding time to progression and progression-free survival were not part of the initial design of the study and are not available.

Patient Population

Patients with newly diagnosed, histologically confirmed GBMs (WHO Grade IV astrocytoma) were included in this study. Patients who were pregnant, tested positive for human anti-mouse antibody assay (HAMA), and had metastatic disease, a second primary cancer, or an iodine allergy were excluded. All patients signed informed consent, and the study was approved by the hospital’s ethics committee and the institutional review board. The historical control group was a retrospective review of patients with GBM who did not enter the study during this time period. Since all patients with newly diagnosed GBMs were offered the study, the historical control group consisted of patients who declined or were not eligible.

Radioimmunotherapy Treatment

The 125I-425 mAb was made by labeling 3.2 mg of 425 murine mAb (provided by the Wistar Institute of Anatomy and Biology) with 50 mCi (1.8 MBq) of 125I by the iodogen method as described previously. Adjuvant 125I-425 mAb was given as 3 weekly intravenous injections of 50 mCi (1.8 MBq), totaling approximately 150 mCi (5.4 MBq) 4–6 weeks after completion of surgery and radiation therapy. Diphenhydramine 25 mg intravenously was given prior to each 125I-425 mAb injection to prevent any potential undetected allergic reaction. Human anti-mouse antibody assay and delayed hypersensitivity skin testing were required prior to each treatment to detect any potential allergic reactions to the treatment. Patients with positive HAMA or a positive skin test did not receive any further treatment. To prevent free 125I uptake in the thyroid, all patients received thyroid blockade with daily supersaturated potassium iodine solution 3 days prior to and 3 days after treatment with 125I-425 mAb. Patients were treated with surgery, radiotherapy, and chemotherapy at the discretion of their neurosurgeon, medical oncologist, and radiation oncologist.

Outcomes and Patient Assessments

All patients in the study were monitored closely for 2 hours after 125I-425 mAb injection. They had clinical evaluations at monthly intervals up to the 6th month, then every 3 months for up to 18 months, then every 6 months after completing antibody therapy. All patients underwent brain imaging every 2 months up to the 6-month evaluation, then at 3-month intervals up to 24 months. Toxicity was recorded per the Cooperative Group Common Toxicity Criteria. If any treatment-related Grade 3 or 4 toxicity was observed, no further treatment was given.

Patient survival was analyzed using the Kaplan-Meier method with 2-sided log-ranked statistics. The Cox proportional hazards model was fitted to adjust for stratification factors and other confounding variables. Statistical analysis was performed using a commercially available program (IPSS version 15, IPSS, Inc.).

Results

Patient and Treatment Characteristics

Between 1987 and 2007, 192 patients with GBM en-
rolled into the study and were treated at Hahnemann University Hospital. Patient and treatment characteristics are illustrated in Table 1. Overall, the median age was 53 years (range 19–78 years), the median KPS score was 80 (range 60–100), 149 patients (77.6%) underwent debulking surgery, 190 (99.0%) received radiation therapy with a median dose of 60 Gy, and 60 (31.3%) were treated with temozolomide. Among 60 patients (31.3%) who received non–temozolomide based chemotherapy, 59 (30.7%) received nitrosourea-based chemotherapy. No chemotherapy was given to 73 patients (38%). All patients received 125I-425 mAb. The median total dose of 125I-425 mAb was 150 mCi, and 18.2% of patients received less than a total dose 120 mCi. The median time from radiation therapy to 125I-425 mAb treatment was 6 weeks.

Among these 192 patients, 132 were treated with 125I-425 mAb alone (RIT), and 60 were treated with 125I-425 mAb and temozolomide (TMZ+RIT). During this same time period, 81 additional patients with GBMs who did not enter the study or receive 125I-425 mAb served as a historical control group (CTL). Patients receiving 125I-425 mAb were younger than CTL (p < 0.001, Kruskal-Wallis test). Sex distribution was similar among the 3 groups. The median KPS score in the RIT and TMZ+RIT were similar. Unfortunately, the KPS score was not recorded in CTL.

The percentage of patients undergoing debulking surgery was similar in the 3 groups (74% in RIT, 87% in TMZ+RIT, and 70% in CTL). The percentage of patients who received radiation therapy in RIT, TMZ+RIT, and CTL were statistically different (98.5, 100, and 68% respectively, p < 0.001). The median dose of radiation therapy was 60 Gy in all 3 groups. The median dose of 125I-425 mAb received was 150 mCi in both study groups.

**TABLE 1: Patient and treatment characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Groups (192 patients)</td>
</tr>
<tr>
<td>median age in yrs (range)</td>
<td>53 (19–78)</td>
</tr>
<tr>
<td>male</td>
<td>109 (56.8)</td>
</tr>
<tr>
<td>female</td>
<td>83 (43.2)</td>
</tr>
<tr>
<td>median KPS score</td>
<td>80</td>
</tr>
<tr>
<td>no. w/ score ≥70</td>
<td>146 (76)</td>
</tr>
<tr>
<td>no. w/ score &lt;70</td>
<td>46 (24)</td>
</tr>
<tr>
<td>surgery</td>
<td>biopsy only</td>
</tr>
<tr>
<td></td>
<td>debulking</td>
</tr>
<tr>
<td>no. receiving radiation therapy</td>
<td>190 (99)</td>
</tr>
<tr>
<td>median radiation dose (Gy)</td>
<td>60</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>nitrosourea-based</td>
</tr>
<tr>
<td></td>
<td>temozolomide</td>
</tr>
<tr>
<td>median 125I-mAb 425 dose in mCi (range)</td>
<td>150 (26–645)</td>
</tr>
</tbody>
</table>

* Unless mentioned otherwise.

**Survival**

At the time of analysis, 171 (89.1%) study patients were dead, 18 patients were alive, and 3 patients were lost to follow-up. The median survival for all 192 patients was 15.7 months (95% CI 13.6–17.8 months). The 1- and 2-year survivals were 62 and 25%, respectively (Table 2).

The median survival for CTL was only 7.2 months. To account for differences in treatments received between CTL and study patients, we analyzed patients who received surgery and radiation therapy. The median survival in months for CTL (39 patients), RIT (97 patients), and TMZ+RIT (51 patients) were 10.2 (95% CI 8.4–12.0 months), 14.5 (95% CI 12.1–16.7 months), and 20.4 (95% CI 14.9–25.8 months), respectively. The 1-year survival was 33% in CTL, 66% in RIT, and 69% in TMZ+RIT. This trend persisted at Year 2 with 5% survival in CTL, 22% in RIT, and 35% in TMZ+RIT (Table 2).

Overall survival differences between all 3 groups were statistically significant (p < 0.001, Fig. 1). Log-rank Mantel-Cox analysis comparing survival differences between RIT versus CTL (p < 0.001) favored RIT; between TMZ+RIT versus CTL (p < 0.001) favored TMZ+RIT; and between TMZ+RIT versus RIT (p = 0.011) favored TMZ+RIT. These differences in survival were confirmed using Breslow generalized Wilcoxon analysis. On multivariate analysis controlling for age, surgery, and radiotherapy, using proportional hazards, the hazard ratio for TMZ+RIT versus RIT was 0.49 (95% CI 0.34–0.69, p < 0.001), TMZ+RIT versus CTL was 0.30 (95% CI 0.20–0.46, p < 0.001), and TMZ+RIT versus RIT was 0.62 (95% CI 0.43–0.89, p = 0.008) (Table 3).

**Toxicity**

Of 192 patients treated with anti-EGFR radioimmuno-therapy, 7 (3.6%) had acute side effects. Three patients developed transient flushing, 2 patients had Grade 1 nausea, 2 patients had Grade 1 hypotension, 3 patients had Grade 1 skin irritation at the injection site, and 4 patients became HAMA positive and received no further treatment. No patient required hospitalization or had Grade 3 or 4 toxicities with the administration of 125I-EGFR mAb. One patient developed a seizure 2 days after receiving treatment and received no further therapy due to progressive disease. In patients receiving temozolomide, no additional toxicity was observed.

**Discussion**

This Phase II study represents the largest reported series using radioimmunotherapy for the treatment of...
Anti-EGFR radioimmunotherapy for glioblastoma multiforme

GBM. Treatment with 125I-425 mAb was well tolerated, and the median survival was 15.7 months. On subgroup analysis of patients who underwent debulking surgery and radiation therapy, treatment with both 125I-425 mAb and temozolomide had greater median, 1-year, and 2-year survival when compared with 125I-425 mAb alone and when compared with historical controls. Treatment with 125I-425 mAb alone had median survival of 14.5 months. Combination 125I-mAb 425 and temozolomide provided the greatest survival benefit with a median survival of 20.4 months. This combination was safe and well tolerated with little added toxicity.

The current study spans over 20 years, and a review of treatment changes and advancements during this time period is warranted. Prior to the 2005 landmark EORTC/NCIC study, despite advancements in surgical and radiation techniques and chemotherapy development, there had been minimal progress in outcomes in patients with GBMs. In 1978, radiation therapy established its role in prolonging survival when doses are greater than 60 Gy, which was confirmed in several randomized control trials. Since then, variations of dose intensification and radiation techniques such as brachytherapy or stereotactic radiotherapy have not shown any survival benefit in randomized cooperative group trials. Maximal resection has been accepted by most surgeons as standard of care based on predominantly retrospective data. Until 2003 and again in 2006, there had been no randomized trial showing the benefit of gross-total resection. Randomized studies examining the role of adjuvant chemotherapy showed mixed and conflicting results. A meta-analysis by the Glioma Meta-Analysis Trialist Group of 12 randomized trials (1900 patients) conducted between 1969 and 1997 examining surgery and radiation therapy with or without non–temozolomide adjuvant chemotherapy showed a median survival of less than 12 months, with modest improvements in 1-year (from 35 to 41%) and 2-year (from 9 to 15%) survival. In comparison, prior to 2002 and prior to the use of temozolomide, the current study had 97 patients treated with adjuvant 125I-mAb 425. The median survival was 14.5 months, and the survival rates were 66 and 22% at 1 and 2 years, respectively.

The results of the current study also have been promising compared with more recent published Phase II and III trials. A PubMed review of newly diagnosed GBM Phase II trials with more than 50 patients since the year 2000 found 12 trials with median survivals ranging from 9.3 to 17 months. Two recent large randomized Phase III trials, SWOG 9503/NCCCTG 937353 and ECOG 2394, did not show survival benefit with experimental treatments, and survivals ranged from 11 to 12 months. The best survival was reported by EORTC/NCIC, in which patients treated with temozolomide had an overall survival benefit with median survival of 14.6 months, and patients with MGMT promoter methylation had the most benefit with median survival of 21.7 months. Although direct comparison between different studies cannot be made, our Phase II study had a comparable 15.7-month overall median survival: 14.5 months in patients treated with 125I-mAb 425 alone, and 20.4 months in those treated with combination 125I-mAb 425 and temozolomide, irrespective of MGMT promoter methylation status (Table 4).

This study is limited to the usual biases of an open-label single-arm Phase II study. In addition, subgroup analysis and comparisons with the historical control group are performed post hoc and are another source of bias. As exemplified by the poor median survivals of the historical control group, patients who entered into the study had better prognosis; they were younger and were more likely to have debulking surgery and radiation therapy. The control group may be older with more advanced disease, leading to an inability to complete treatment or participate in the Phase II trial. We made our best attempt to account for such differences in patient characteristics by controlling for age and treatments received. Direct statistical comparisons between the historical control and the study group were unplanned, and these results serve mainly as a source of perspective.

TABLE 3: Survival comparison

<table>
<thead>
<tr>
<th>Group</th>
<th>Log Rank (Mantel-Cox)</th>
<th>Multivariate HR* (95% CI), p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIT vs CTL</td>
<td>p &lt; 0.001</td>
<td>0.49 (0.34–0.69), p &lt; 0.001</td>
</tr>
<tr>
<td>TMZ+RIT vs CTL</td>
<td>p &lt; 0.001</td>
<td>0.30 (0.20–0.46), p &lt; 0.001</td>
</tr>
<tr>
<td>TMZ+RIT vs RIT</td>
<td>p = 0.011</td>
<td>0.62 (0.43–0.89), p = 0.008</td>
</tr>
</tbody>
</table>

* Controlling for age, resection, and radiation therapy.

TABLE 4: Comparison of median survival in the present study with that in the EORTC/NCIC study

<table>
<thead>
<tr>
<th>Current Study (no. of patients)</th>
<th>Median Survival (mos)</th>
<th>EORTC/NCIC (no. of patients)</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL (39)</td>
<td>10.2</td>
<td>radiation alone (286)</td>
<td>12.1</td>
</tr>
<tr>
<td>RIT (192)</td>
<td>15.7</td>
<td>temozolomide (287)</td>
<td>14.6</td>
</tr>
<tr>
<td>TMZ+RIT (51)</td>
<td>20.4</td>
<td>methyl-MGMT (46)</td>
<td>21.7</td>
</tr>
</tbody>
</table>
Conclusions

In patients with newly diagnosed GBM, treatment with 125I-425 mAb with or without temozolomide is safe and well tolerated. Overall survival is highly promising when compared with historical controls and reports from large cooperative group investigations. Further investigation of 125I-425 mAb 425 treatment outcomes may help optimize future treatment regimens.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: L Li, TS Quang, JH Kim, LW Brady. Acquisition of data: L Li, TS Quang, JH Kim, JG Emrich, TE Yaeger, JM Jenrette, SC Cohen, P Black, LW Brady. Analysis and interpretation of data: L Li, TS Quang, EJ Gracely, JG Emrich, JH Kim, TE Yaeger, JM Jenrette, SC Cohen, P Black, LW Brady. Drafting the article: L Li, TS Quang, LW Brady. Critically revising the article: L Li, TS Quang, EJ Gracely, JH Kim, JG Emrich, TE Yaeger, JM Jenrette, SC Cohen, P Black, LW Brady. Statistical analysis: L Li, EJ Gracely, LW Brady. Administrative/technical/material support: JG Emrich. Study supervision: LW Brady.

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Address correspondence to: Linna Li, M.D., Department of Radiation Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, Pennsylvania 19111. email: linna.li@fccc.edu.