Editorial

Is re-radiation for glioblastoma after progression associated with increased survival: to treat or not to treat?

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Glioblastoma is the most common malignant brain tumor, representing 53.8% of all gliomas (1). Despite standard of care treatment with radiation and temozolomide chemotherapy, glioblastoma has a dismal prognosis with median survival of 14.6 months (2) and 20.9 months with addition of tumor-treating fields (Optune) (3). After tumor progression, treatment with re-irradiation and/or systemic therapy has yet to show improved overall survival leading to disagreement as to the best management of the patient who has progressed after standard of care treatment.

We read the article by Shi *et al.* (4) with great interest and would like to thank the authors for attempting to shed light on the optimal treatment for recurrent glioblastoma. The authors analyzed 637 patients from the RTOG 0525 study (5) with newly diagnosed glioblastoma treated with dose-dense temozolomide who had information regarding their management after tumor progression. The study divided patients in 4 groups according to their non-protocol management after progression, evaluating those that received radiation treatment alone, systemic therapy alone, radiation and systemic therapy, and patients who received neither radiation nor systemic treatment. Their analysis suggests that there was significant survival benefit among patients receiving any salvage therapy (radiation alone 8.2 months, systemic therapy 10.6 months, and both radiation and systemic therapy 12.2 months) compared to those who received no treatment (4.8 months) after progression.

There remains no consensus on the optimal treatment of glioblastoma after progression, with many prospective studies failing to show survival benefit at recurrence even with Food and Drug Administration approved therapies such as bevacizumab or tumor-treating fields (6-8). The phase II trial by Vredenburgh *et al.* with bevacizumab plus irinotecan in recurrent glioblastoma showed a 6-month overall survival of 77% (7). Likewise, Friedman *et al.* were able to demonstrate a median overall survival of 10.7 months for those receiving bevacizumab and irinotecan (8).

The BELOB trial was on open-label trial for second-line chemotherapy where patients were randomized to receive bevacizumab, lomustine, or combination bevacizumab and lomustine (9). The patients receiving combination bevacizumab and lomustine had an overall 9-month overall survival rate of 63%, which was superior to the bevacizumab alone group of 38%, or 43% in the lomustine alone group. Shi *et al.* provide support for continued therapy beyond standard of care chemoradiation. Information on the specific agent or regimen delivered was known for only 54% of patients who received non-protocol systemic therapy, and details on type of radiation therapy after recurrence were not provided in the study (4). Thus, particular chemotherapy agents of benefit are unable to be elucidated from the article. Only clear finding was that those with no salvage treatment had the poorest survival among the four arms in the study.

Similarly, various retrospective studies evaluating the therapeutic contribution to stereotactic radiosurgery and bevacizumab after progression have shown survival and progression free survival benefit (10,11). The article by Shi *et al.* provides a larger retrospective analysis of patients treated with radiation therapy after progression in

prospective phase III randomized trial, however, it remains limited by its retrospective nature. Additionally, the study suffers from relatively small patient population in some treatment groups. The analysis of 637 patients from RTOG 0525 was robust, however, their sub-analysis revealed only 64 patients who received both radiation and systemic therapy, and 24 patients who received radiation alone. There is limited data to draw a conclusion about how these subjects compare to their counterparts who did not receive re-irradiation.

Moreover, the finding that salvage treatment was associated with longer survival, may merely reflect the poor performance status of those who were not treated with salvage therapy. Patients with favorable performance status (KPS >70) in those receiving radiation therapy only was less common than in patients receiving both radiation therapy and systemic therapy, 71 % *vs.* 92%, respectively. The higher percentage of favorable Karnofsky performance status (KPS) in those receiving combined radiation and systemic therapy suggests an overall poorer performance status in radiation only group compared to the combined treatment group. Likewise, those with no neurologic symptoms at randomization was higher in the combined therapy group as compared with the radiation therapy only treatment group, 42% *vs.* 25%, respectively. The RT only group has no survivors at 24 months as compared with all other groups, which is unexpected, and may reflect the patient population having a poorer performance status and neurologic symptoms.

Secondly, the author's analysis of the RTOG 0525 study also found that after progression there did not appear to be a significant difference among patients receiving systemic or combined therapy compared to radiation alone. Survival models controlling for potential confounders showed that radiation alone had only modestly better survival (HR 0.74) compared to those that underwent systemic therapy either with (HR 0.44) or without radiation therapy (HR 0.42). In the study, no survival difference was seen between radiation only and those receiving systemic therapy either with radiation or alone. The optimal treatment of recurrent glioblastoma is yet to be established, making this evaluation of re-irradiation notable.

The sub-analysis of the RTOG 0525 study by Shi *et al.* provides support to additional treatment beyond tumor progression in glioblastoma patients treated with standard chemoradiation. Notably in the study, it did not appear to matter if patients had re-irradiation, they could simply receive systemic therapy as adding radiation to systemic therapy or treating with radiation alone have no difference. Or as the author points out, the survival difference in those receiving treatment may merely reflect selection bias against those with poorer expected prognosis and functional status. Clearer longitudinal studies with multiple therapeutic comparison arms are needed to help delineate the optimal treatment patterns in recurrent glioblastoma.

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