

## Pseudoprogression in Glioblastoma

**TO THE EDITOR:** Brandes et al<sup>1</sup> are to be congratulated for their article describing a phenomenon of apparent tumor progression in newly diagnosed patients with glioblastoma (GBM) treated with concurrent temozolomide (TMZ) and radiotherapy (RT). Of 208 patients treated with the regimen, 103 were analyzed for O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) tumor content, radiographic course during therapy, and survival. Several issues regarding the article warrant discussion.

It is unclear why only approximately 50% of patients treated with the regimen were assessable for tumor MGMT content, given that it seems to stratify patients with GBM into a subsets benefiting (patients with low MGMT expression) or not (patients with high MGMT expression) from the addition of adjuvant TMZ.<sup>2</sup> In addition, the rationale for 12 months of post-RT TMZ is perplexing, given that the regimen as originally recommended used 6 months of post-RT TMZ,<sup>2</sup> and the current trends in lung cancer and non-Hodgkin's lymphoma treatment are to administer adjuvant chemotherapy for a shorter duration without compromising efficacy. Lastly, the standard 5 consecutive days of TMZ administered every 28 days postradiotherapy TMZ schedule does not durably affect MGMT tumor content.<sup>3</sup>

Pseudoprogression, in retrospect, was originally described by Hoffman et al<sup>4</sup> and revisited by de Witt et al<sup>5</sup> in patients with newly diagnosed GBM treated with RT and with or without carmustine. Of patients observed to experience disease progression immediately after RT (28% to 51% of the total), 28% to 33% (9% to 14% of the total) were shown subsequently to have either improved or stable brain imaging. In 2006, Chamberlain et al<sup>6</sup> characterized this phenomenon (in the context of the TMZ regimen) pathologically: all symptomatic patients who were considered candidates for surgery underwent second resection. Of the 50% of patients with progressive disease, nearly half were treated surgically (25% of the total), among whom half (14% of the total) demonstrated treatment injury without identifiable GBM. Pseudoprogression was characterized as occurring predominantly (58%) within the first 3 months of completing RT plus TMZ, but not exclusively, because nearly one third of patients were seen 3 months after completion of RT plus TMZ. The study by Chamberlain et al<sup>6</sup> postulated that pseudoprogression was not uncommon with RT plus TMZ and likely underestimated in this article because pseudoprogression was defined pathologically. It was postulated that pseudoprogression may represent an exaggerated response to effective therapy, may lead to a nonindicated change in therapy (including no therapy) or unnecessary surgery (though is appropriate in symptomatic patients with significant mass effect), and may create a false-positive response

rate to subsequent therapy. Taal et al<sup>7</sup> reported early recurrence in 35% of patients, among whom radiographic improvement was seen in half (18% of the total). de Witt et al,<sup>5</sup> Taal et al,<sup>7</sup> and Brandes et al<sup>1</sup> all characterized pseudoprogression by early disease recurrence seen immediately post-RT plus TMZ with improvement or stabilization after 2 months. In contrast to the Chamberlain et al study, no patient underwent a resection, although Brandes et al suggests that on average, 7 months was required for clinical resolution of pseudoprogression. In addition and in contrast to the above-mentioned study, no functional brain imaging (magnetic resonance spectroscopy, magnetic resonance perfusion, or [<sup>18</sup>F]fluorodeoxyglucose positron emission tomography) were performed in an attempt to resolve true progression from pseudoprogression.

These comments are not meant to diminish the results of this elegant study, notable for determination of the frequent incidence of pseudoprogression in TMZ responsive tumors defined by low MGMT content and the improved overall survival in patients with pseudoprogression. Rather, the comments reflect the challenges encountered in treating patients with GBM and the difficulty in clinically distinguishing pseudoprogression from true progression.

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### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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**IN REPLY:** We thank Drs Chamberlain and Glantz for their interest in our article on the incidence and outcome of pseudoprogression after concurrent chemoradiotherapy in glioblastoma (GBM) patients in which, for the first time, a correlation was found with O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) methyl-

ation status.<sup>1</sup> In the study, 208 patients were treated with combined radiotherapy and temozolomide (TMZ), but MGMT methylation status was only assessable in 103 patients; the remaining 105 patients had insufficient histologic material or MGMT was not assessable at methylation-specific polymerase chain reaction. However, as shown