

Pseudoprogression in Glioblastoma

TO THE EDITOR: Brandes et al¹ 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 O⁶-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.² 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,² 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.³

Pseudoprogression, in retrospect, was originally described by Hoffman et al⁴ and revisited by de Witt et al⁵ 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 al⁶ 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 al⁶ 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 al⁷ reported early recurrence in 35% of patients, among whom radiographic improvement was seen in half (18% of the total). de Witt et al,⁵ Taal et al,⁷ and Brandes et al¹ 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 [¹⁸F]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 O⁶-methylguanine-DNA methyltransferase (MGMT) methyl-

ation status.¹ 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

by Hegi et al,² patients whose samples are not assessable for MGMT methylation do not seem to characterize a specific subset with a different survival; data collected from these patients therefore do not result in any bias. We do not agree with the authors' claim that there is a potential logical correlation between MGMT gene promoter methylation and MGMT protein expression: given that MGMT, an inducible enzyme, may be upregulated after chemotherapy or radiotherapy, the concept of low/high MGMT expression should be avoided in this context.

Drs Chamberlain and Glantz appropriately raised the question concerning the concept of adjuvant treatment in GBM, developed in the 1970s with a goal of increasing the cure rate after the complete excision of tumors such as breast cancer, the underlying rationale being to treat microscopic disease when the tumor bulk was at a minimum. However, GBM patients rarely received "true" adjuvant treatment and, in the European Organisation for Research and Treatment of Cancer (EORTC) National Cancer Institute of Canada trial, only 49% of patients underwent complete resection.³ In our protocol, like those for metastatic disease in other solid tumors, treatment was scheduled up to disease presence, or given in 12 cycles when no disease was found during magnetic resonance (MR) imaging or a complete response was achieved. Furthermore, the proposed administration of 12 cycles was included in the Canadian recommendations for the treatment of GBM, at least for patients who showed continuous improvement on therapy,⁴ and this schedule has been suggested as a standard arm in the new experimental protocols of the major international cooperative groups, such as EORTC and Radiation Therapy Oncology Group (ie, EORTC 26052-22053/Radiation Therapy Oncology Group 0525 trial, comparing standard treatment with dose-intensive TMZ in patients with newly diagnosed GBM).

Moreover, Drs Chamberlain and Glantz stated that the standard 5 days every 28 days postradiotherapy TMZ schedule does not have a long-term effect on MGMT tumor content. However, as shown by the references made, the few data available concerning this finding are reported in a study evaluating MGMT inactivation in peripheral-blood mononuclear cells treated with TMZ,⁵ but whether this also applies to tumor cells remains to be demonstrated.⁶ To date, no data are available on the advantages of a prolonged/alternative schedule versus the standard schedule of 5 days every 28 days.

The authors suggest that histology is the valid method for identifying pseudoprogression; yet, as they state, only a small percentage of patients with suspected pseudoprogression undergo surgery because the tumor mass, which can be controlled by corticosteroids, tends to diminish quite rapidly. Moreover, it is difficult to define the role of necrosis given that, in the histologic setting, it is often present concomitantly with neoplastic cells. Lastly, the role of new imaging tools such as spectroscopic MR imaging, MR scan, MR perfusion and diffusion, or [¹⁸F]fluorodeoxyglucose positron emission tomography in discriminating disease progression and pseudoprogression have recently been reviewed.⁷ A few of our patients underwent repeat surgery, and others underwent brain functional imaging; however, due to the sporadic nature of this treatment option and the bias in patient selection, no conclusion can be drawn regarding the role of these diagnostic modalities, which should be tested in prospective trials.

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Genomics and Challenges Toward Personalized Breast Cancer Local Control

TO THE EDITOR: The article by Nguyen et al¹ in *Journal of Clinical Oncology* demonstrates an overall low local recurrence rate after breast-conserving surgery, but varying magnitude of this risk among gene expression profiling–based subtypes. The 5-year local recurrence rates of 793 patients were higher for HER-2 (8.4%) and basal (7.1%) subtypes than for luminal A (0.8%) or luminal B (1.5%) subtypes. Approximating this molecular classification using human epidermal growth factor receptor 2 (HER-2), estrogen receptor (ER), and progesterone receptor (PR) status currently used in routine clinical practice,² the authors provide clinically useful information on a potential link among these subtypes and local control.

Why is local control important for long-term survival given the systemic nature of breast cancer? Local failures include local recurrence or a new ipsilateral breast cancer and contralateral breast cancer. With an increasing number of long-term survivors and long-term follow-up data available, objective evidence documents that ipsilateral breast cancer and/or contralateral breast cancer as first isolated events may be associated with increased mortality.³⁻⁵

Potential pretreatment risk stratification into high, moderate, and low risk for local failure may affect treatment decision. High-risk patients may benefit from a more aggressive surgery, such as unilateral mastectomy and contralateral prophylactic mastectomy rather than the standard breast-conserving surgery for localized disease. Recent data show a dramatic increase of more aggressive surgery in the United States to prevent this local failure.⁶ Instead, this generalized surgical overtreatment, a personalized aggressive surgery only to high-risk patients, may prevent local failure and improve survival in these