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Clinical end points in recurrent glioblastoma: are antiangiogenic agents friend or foe?

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Enrico Franceschi

Department of Medical Oncology, Bellaria-Maggiore Hospital, Azienda USL, Bologna, Italy

Alba A Brandes

Author for correspondence:
Department of Medical Oncology, Bellaria-Maggiore Hospital, Azienda USL, Bologna, Italy
Tel.: +39 051 622 5102
Fax: +39 051 622 5057
alba.brandes@yahoo.it

“...targeting VEGF with bevacizumab may reduce contrast leakage into the tumor, thus giving rise to neuroradiological images of increased radiographic response and/or pseudoresponse.”

The challenge involved in treating recurrent glioblastoma (GBM), which continues to be invariably fatal, is complicated by the rapid worsening of the neurological and psychological condition of patients with this disease.

Since the incorporation of temozolomide in ‘the backbone’ of first-line treatment for newly diagnosed GBM patients, as shown in the randomized Phase III European Organisation for Research and Treatment of Cancer 22981/26981-NCIC CE.3 (EORTC/NCIC) trial, there are few valid options for patients when recurrence is diagnosed [1]. Nitrosoureas, the cornerstone of first and second-line brain tumor treatment for at least 20 years, have been found, in this modern age, to confer a progression-free survival at 6 months (PFS-6) ranging from 19 to 24% with chloroethylcyclohexylnitrosourea [2,3] and 21% with fotemustine [4].

“...the European Medicines Agency denied approval for the administration of bevacizumab in this clinical setting...”

Recent years have seen the development of novel approaches in medical oncology, and antiangiogenic treatments now play an important role in the treatment of cancer of the colon–rectum, kidney, breast and lung. Preclinical data indicate that the proliferation and survival of malignant

glioma cells depend on angiogenesis, and the VEGF pathway appears to play a particularly important role in this process [5]. In a preliminary study in 2005, a rate of 66% and limited toxicity were reported in 29 cases of recurrent malignant glioma following treatment with the VEGF-neutralizing antibody, bevacizumab, administered in combination with irinotecan [6]; other groups published data from retrospective and/or prospective studies using this compound as a single agent or in a combined regimen, and reported response and PFS-6 rates ranging from 20 to 60% and 25 to 50%, respectively [7–11]. These data, considered a breakthrough in neuro-oncology, raised the interest of the scientific community. Based on the durable objective response rates observed in the AVF3708g and NCI 06-C-0064E trials [8,11], which evaluated the role of bevacizumab alone or combined with irinotecan, the US FDA granted accelerated provisional approval for the use of bevacizumab as a single agent in patients with GBM. However, since VEGF regulates vascular permeability, targeting VEGF with bevacizumab may reduce contrast leakage into the tumor, thus giving rise to neuroradiological images of increased radiographic response and/or pseudoresponse. Thus, the decrease in contrast enhancement compromised the reliability of any assessment of disease response, calling for further improvement

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in the neuroradiological diagnostic approach [12]. Therefore, the European Medicines Agency denied approval for the administration of bevacizumab in this clinical setting, claiming that the number of patients who responded to treatment was limited and that response rates may not be a suitable measure of the efficacy of the drug [101]. Moreover, the overall survival (OS) rates of 7–10 months obtained in Phase II studies were hardly promising, especially in light of the high radiological response rates (28–35%) and the progression-free survival (PFS) rates obtained (29–43%).

“...assessment of the disease, in particular its progression, continues to be unreliable in patients with recurrences who are administered antiangiogenic agents and, as a consequence, any evaluation of the results from clinical trials is biased.”

The new Response Assessment Criteria in Neuro-Oncology (RANO) [13], developed in order to overcome the potential disadvantages of the classical MacDonald's response evaluation criteria [14], stressed the importance of the use of steroids and the patient's clinical status in assessing response, and called for the evaluation of T2/FLAIR alterations, as well as contrast-enhancement modifications with a view to detecting pseudoresponses and nonenhancing disease progression during antiangiogenic treatment. In fact, any decrease in vascular permeability can lead to a reduction in contrast extravasation and, consequently, contrast enhancement, irrespective of any change in tumor dimensions. Unfortunately, no prospective validation of these criteria has yet been made, and nor are sound data available on the utility of the rate of T2/FLAIR modifications [15], whose pattern can also be altered by factors such as radiotherapy, decreased corticosteroid dosing, demyelination, ischemic injury and infection.

Therefore, assessment of the disease, in particular its progression, continues to be unreliable in patients with recurrences who are administered antiangiogenic agents and, as a consequence, any evaluation of the results from clinical trials is biased. This raises the issue of consistent clinical end points for Phase II trials.

In order to improve upon the treatment available for GBM patients, clinical trials must be designed to yield information that is immediately useful in the therapeutic decision-making process, as well as in providing patient care. The method for assessing the activity of a drug (OS, response rate, PFS) should neither penalize the patient population nor slow the progress of evaluating the drug for approval. It is therefore of utmost importance that trials have a realistic and reliable primary end point.

Until recently, the response rate was not a primary end point in Phase II studies on high-grade gliomas since it is particularly difficult to evaluate response in neuro-oncology, brain imaging being based on the phenomenon of contrast extravasation, which is indirect evidence of the neoangiogenesis typical of high-grade gliomas. In the 1990s, neurological conditions and corticosteroid

administration, indirect signs of brain tumor modification and peritumoral edema variations, were therefore included in the criteria for response assessment [14].

In the pre-antiangiogenic treatment era, PFS-6 was considered the best possible end point in Phase II trials on recurrent GBM treated with chemotherapy, since it reflects the rate of cases of durable disease control, this clinically relevant end point not being influenced by further sequential treatments following disease progression. However, thanks to the introduction of antiangiogenic agents, this paradigm has changed, and the best possible end point for assessing the efficacy of an antiangiogenic agent for Phase II trials in this age has yet to be established.

Moreover, PFS as an end point shares several limitations with all progression-based end points [16]: frequent radiological assessments are required, with a consequent increase in the risk of measurement error and bias [17], as well as compromising PFS findings. Both the USA FDA and European Medicines Agency recommend blinded independent adjudication of assessments [18,19]. Since PFS can vary depending on evaluation time bias (i.e., differences in evaluation times) [17], it is important to establish appropriate time points for measuring progression, as well as clear guidelines for interpreting nonenhancing lesion modifications.

“In the pre-antiangiogenic treatment era, progression-free survival at 6 months was considered the best possible end point in Phase II trials on recurrent glioblastoma treated with chemotherapy...”

Furthermore, neither of the conditions proposed for an intermediate end point to be considered as an acceptable surrogate for the primary clinical end point (strong association between the effect of treatment on the surrogate and the true end point; or the surrogate end point and the true end point [i.e., OS]) have been satisfied by PFS for antiangiogenic agents in the recurrent GBM, since the real effect of treatment is masked by the effects of antiangiogenic agents on blood–brain barrier permeability, which decreases contrast enhancement extravasation (pseudoresponses) [20]. Moreover, the correlation between PFS and OS established in recurrent GBM patients treated with cytotoxic drugs [21] has also been confirmed in patients with recurrences after combined chemoradiation [22]. However, it is unclear whether an attempt should also be made to confirm this correlation in patients treated with antiangiogenic agents, since the correlation between PFS and OS has frequently been overlooked in the numerous trials conducted on patients with many different types of cancer treated with bevacizumab [23].

Prolonged OS, which represents the greatest possible clinical benefit, is unambiguously defined and meaningful to patients, and has numerous advantages as an end point. First, it can be assessed easily and accurately, with 100% accuracy for the event and nearly 100% accuracy for the time of the event. Survival can be assessed on a daily basis, rather than at predetermined intervals, and is easily documented through direct contact and confirmed

through registries. Second, statistically significant improvements in OS are considered clinically significant, provided the drug does not incur unacceptable toxicity [13].

However, the measurement of OS can also be skewed by the effects of subsequent therapies, which can lead to an underestimation of the efficacy of an experimental agent. This applies in particular to cancers for which several active anticancer drugs are available, such as colon, breast, kidney and lung cancer. On the other hand, recurrent GBM tends to progress rapidly and third-line treatment can be delivered in only a small percentage of patients, therefore probably not having a significant effect on survival; in this case, PFS has no clear advantage over OS as a parameter of drug efficacy.

One concern with OS as the primary end point in recurrent GBM is that the period of observation required before analysis is complete is longer than that required for PFS. However, this problem should be overcome by using OS rates and, in particular, the OS rate at 6 months, for which the observation of events remains the same.

While reliable measures of disease progression are important in indicating the treatments to be studied in trials, clinical-outcome trials must continue to be the fundamental source for informing clinicians on which treatments improve clinical outcomes.

Therefore, in the field of neuro-oncology, when evaluating the role of antiangiogenic agents the use of neuroradiological measures of disease progression as primary end points should also be avoided in Phase II trials; these measures should be replaced by OS rates [15].

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