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Review

Appropriate end-points for right results in the age of antiangiogenic agents: Future options for phase II trials in patients with recurrent glioblastoma

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ABSTRACT

The progression-free survival rate at 6 months (PFS-6) has long been considered the best end-point for assessing the efficacy of new agents in phase II trials in patients with recurrent glioblastoma. However, due to the introduction of antiangiogenic agents in this setting, and their intrinsic propensity to alter neuroradiological disease assessment by producing pseudoregression, any end-point based on neuroradiological modifications should be reconsidered. Further, statistically significant effects on progression-free survival (PFS) only should not automatically be considered reliable evidence of meaningful clinical benefit. In this context, because of its direct and unquestionable clinical relevance, overall survival (OS) represents the gold standard end-point for measuring clinical efficacy, despite the disadvantage that it is influenced by subsequent therapies and usually takes longer time to be evaluated. Therefore, while awaiting novel imaging criteria for response evaluation and/or new imaging tools to distinguish between 'true' and 'pseudo'-responses to antiangiogenic agents, the measurement of OS or OS rates should be considered primary end-points, also in phase II trials with these agents.

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1. Introduction

The choice of the appropriate end-point in clinical trials regularly gives rise to controversy. As a general rule in curative-intent therapy, overall survival (OS) is the ultimate gold standard, while in palliative-intent treatment the aim is at least prolonging OS while conserving or improving the quality of life (QoL). However, the tools to objectively and reproducibly assess QoL are limited with a high interpatient variability.

Phase II trials generally attempt to see if a novel drug or a novel combination of agents is promising, with the final objective to test them in a full phase III trial. These phase II trials typically have a well established surrogate end-point that if met, reflects likely clinical benefit leads to further drug development. Surrogate end-points are implemented to assess the potential benefit of treatments and to speed up a risk–benefit evaluation (as well as clinical development). Tumour response is commonly used as a valid (albeit not always validated) surrogate end-point. In primary brain tumours however, evaluation of treatment efficacy is complicated by limitations of imaging, frequent absence of overt tumour regression or only delayed tumour regression while treatment is still providing some benefit to the individual patient. This observation and the low response rates even in seemingly effective agents lead to the introduction of the 6 months progression free survival (PFS-6) end-point in phase II trials on glioblastoma (GBM). Imaging of brain tumours however is a cause of potential problems that need to be realised. Imaging of high grade brain tumours commonly focuses on contrast enhancement detected by T1-weighted magnetic resonance imaging (MRI) that is influenced by disruption of the blood–brain barrier (BBB). Many novel anti-angiogenic agents will modify vascular permeability and therefore contrast-enhanced imaging substantially, without necessarily reflecting changes in tumour growth or extension. These agents are being increasingly investigated in brain tumours, thus there is an even greater need to improve our understanding and tools in measuring antitumour activity. Without validation, even the modified Macdonald criteria[1,2] that qualitatively integrate T2 changes as well as the an integration with more sophisticated magnetic resonance imaging (MRI) techniques like diffusion- (DWI) or perfusion-weighted (PWI) imaging or MR spectroscopy (MRS) may not solve this issue. As a consequence, while phase II trials on chemotherapy should continue the use of the classical PFS-6 as the primary end-point, trials on antiangiogenic agents may require different end-points.[3]

2. End-points in neuro-oncology

When deciding on if and how to treat an individual patient, physicians base their judgment on a multitude of indicators; factors reflecting the patients general status and ability to tolerate therapy (performance status) and factors indicating treatment efficacy by prolongation of life, improving or delaying deterioration of neurological functioning and QoL, avoidance of disease-related complications and finally cost. Effectiveness can be defined by the effect of treatment on clinical outcome or, in some cases, by biologic and imaging markers.

The importance of the BBB on the imaging of brain tumours and its modification by the administration of corticosteroids was already recognised over 20 years ago by Macdonald and colleagues.[1] Their proposed modification of the 2-dimensional WHO response criteria by consideration of steroid dose changes (an increase in steroid dosing due to clinical deterioration may be accompanied by reduced contrast enhancement)[4] and neurological function in addition to tumour size has since been generally adopted and is referred in the literature as the Macdonald criteria.[1] Only tumour shrinkage documented by a 50% reduction of the contrast-enhancing lesion on CT or MRI in bi-dimensional diameters with a stable or decreasing dose of corticosteroids and an at least stable neurological function is considered a partial response. Nevertheless, many clinical reports still include minor responses or disease stabilisation as a 'response'. Although disease stabilisation may indeed be a worthwhile objective allowing to postpone gradual neurological deterioration, this should be reported as disease control-rate (PFS-rate) rather than as a response.

In neuro-oncology, tumours that display contrast enhancement on imaging do so as a consequence of contrast extravasation in tumoural vessels. These abnormally leaky vessels are the product of neoangiogenesis and are characteristic although not specific of high-grade tumours. Anti-angiogenic and vasculature-modifying agents modify vascular permeability and interstitial pressure, and thus the extent and distribution of gadolinium extravasation. These imaging changes may not necessarily reflect tumour size, and a reduction of contrast extravasation may purely reflect vascular changes.[3,5] Although images may look improved the actual tumour extension and growth may remain unchanged, a phenomenon termed 'pseudo-response[3]'. Moreover, interruption of the treatment, with the conclusion of this effect on vascular permeability may lead to a rebound resulting in an overestimation of tumour growth.

3. Response rate

Tumour response as determined by imaging is commonly used as a surrogate end-point in therapeutic trials of advanced cancer. Ideally, an imaging marker should indicate response as early as possible, e.g. after the first treatment cycle, and, of course, should correlate with PFS and OS. Unfortunately, tumour response cannot replace survival in ascertaining outcome[6] although there may be great benefit to the patient. A number of factors may explain why response fails to translate into prolonged survival. In solid tumours and lymphoma the achievement of a complete response may be of greater relevance, however in brain tumours and in particular high grade gliomas even partial responses are rarely achieved. Responses are often only short-lived and may be without tangible clinical relevance. Further, inherent toxicity of anticancer agents may adversely affect outcome and counterbalance a potential benefit. Tumour progression may be evaluated more reliably and reproducibly than tumour re-

sponse, this end-point will also capture disease stabilisation into favourable outcome.[7–10]

The evaluation and correlation of response with survival end-points in a large number of patients with newly diagnosed (n = 1359) and recurrent GBM (n = 357) treated prospectively on North Central Cancer Treatment Group trials (phase II and III) of best response (responders versus non-responders) with survival end-points (time to progression [TTP], PFS, and OS) showed that in newly diagnosed GBM tumour response correlated significantly with TTP. The predictive effect for OS was less robust, albeit reaching significance. For recurrent GBM, response was an acceptable surrogate for TTP or PFS, but not for OS.[11] Recently, a landmark analysis of the phase II BRAIN study suggested that response rate (RR) should be correlated with OS.[12] However, due to the lack of validated response criteria for antiangiogenic treatments in neuro-oncology, the relationship between response and OS has to be better investigated.[12]

4. Progression-free survival

PFS as an end-point has the advantage of not being modified by subsequent lines treatments and thus allows to evaluate the direct effect of a therapeutic intervention. However, the assessment and determination of disease progression is susceptible to great variation and lack of precision.

Landmark analysis of the PFS-6 has been used for almost a decade as a surrogate end-point in phase II trials using chemotherapy in gliomas. This end-point combines the more reliable assessment of tumour progression (rather than response, see above) with the advantages of a single assessment at a given time point. It identifies the patients with durable disease control, a clinically important and meaningful goal, and remains the best end-point in phase II trials with chemotherapy. In a retrospective analysis of 225 pooled GBM patients from 8 phase II chemotherapy trials that were all considered negative, a PFS-6 of 15% (95% CI 10%; 19%) and a median PFS of 9 weeks (95% CI 8; 10)[13] were determined as benchmarks for future comparisons. Similar subsequent meta-analyses demonstrated a correlation of PFS-6 with the 1-year OS rate, strongly suggesting that PFS-6 may indeed be a valid surrogate end-point.[14,15] Of note, all these trials were conducted before the area of the current standard of care with concomitant temozolomide-based chemoradiotherapy. The pivotal trials of temozolomide in recurrent GBM used PFS-6 as a primary end-point demonstrating a PFS-6 rate of 18 and 21% (95% CI 11; 29)[8,10], only marginally better than the historical benchmark. Subsequent trials of temozolomide in combination with other agents in chemo-naïve recurrent GBM patients showed PFS-6 rates up to 39% in patients having failed first-line chemoradiotherapy.[16–18] Two recent randomised trials using single agent lomustine as a control showed PFS-6 rates of 19–24.5% (95% CI not reported).[19,20] Similarly, fotemustine, a new generation nitrosourea, has shown a PFS-6 of 21% (95% CI 9–33%).[21]

PFS as an end-point has several limitations[22]: the date at which radiological evaluation confirms progression is only a proxy for true progression time, which lies at some point within the time interval between two successive assessments.[23] The resulting overestimation of median PFS is one reason, which may complicate comparisons across trials since patients may have undergone different evaluation schedules.[24] Frequent radiological assessments are required with inherent potential for measurement error.[23] Both the European Medicines Agency (EMEA) and United States Food and Drug Administration (FDA) recommend independent blinded radiological assessments.[25,26] However, this evaluation at distance from the patient may not appropriately reflect clinical situation and considerations, and should thus be termed radiological PFS assessment. A strict imaging schedule for evaluating progression must be established since PFS will vary depending on frequency of radiological evaluation observation bias (i.e. differences in evaluation times).[23] Moreover inter-observer variability has been demonstrated even inside the same clinical trial. As a paradigmatic example, the *BRAIN* study, that investigated the role of bevacizumab alone or in combination with irinotecan,[27] had undergone 3 different and independent assessments of the same images by local investigators, by the sponsor-mandated central review, and finally by the FDA. RR and PFS determination varied substantially between the reviewers.[28,29] In neuro-oncology, where a combined assessment and expertise of clinical and radiological parameters are required, treatment benefit and occurrence of progression may more accurately be evaluated by expert clinicians, rather than the allegedly 'objective' assessment solely by radiologists.

5. Overall survival

OS remains the gold standard to establish a treatment effect of a new oncological therapy. Although the objective of palliative therapy may be QoL, and, in neuro-oncology, independence in activities of daily living, we lack a reliable and reproducible tool for evaluation. While the surrogate end-points have their inherent limitations in determination, reproducibility and validity, the time to death can be reliably and easily assessed. Survival time as unequivocally determined by the date of death or of last follow-up is easily documented through direct contact with the patient's family and confirmed through registries. Statistically significant improvements in survival are considered clinically meaningful, provided the drug toxicity is acceptable. However, evaluation of a treatment effect by measuring OS may be skewed by the subsequent therapies, and confounded by causes of mortality unrelated to cancer, and does not necessarily reflect improvements in symptom control and maintenance of QoL. Together this may lead to underestimation of the efficacy of an experimental agent or treatment. In recurrent malignant glioma, however, treatment options at recurrence are limited and of modest efficacy, and OS times are few months, thus OS remains the preferred end-point in phase III clinical trials or phase II studies with antiangiogenic treatments. However, when evaluating OS, the stratification of prognostic factors should be taken into account[30] to avoid a patient selection bias. Finally, with respect to PFS-6, OS has the disadvantage of requiring longer patient follow-up. However, by using OS rates (i.e. OS rate at 6 or 12 months – OS6 or OS12), this drawback should be obviated.

6. Anti-angiogenic agents in patients with high-grade gliomas

Malignant gliomas are highly vascularised tumours. Preclinical data indicate that angiogenesis is essential for the proliferation and survival of malignant glioma cells, and the vascular endothelial growth factor (VEGF)-mediated signalling pathways play a key role in tumour vasculature development. After an initial anecdotal report,[31] unprecedented high radiological RRs of up to 66% and PFS-6 rates of 30–50% were repeatedly reported after treatment with the anti-VEGF monoclonal antibody bevacizumab, either as a single agent or in combination with irinotecan[32–36] (Fig. 1). Despite these encouraging signs of antitumour activity, this treatment may not translate into equal prolongation of OS; reported median OS rates range from 7 to 10 months, slightly longer than historical controls (5–7 months) and in the same range as other contemporary phase II trials with targeted agents that were considered negative.[37–39] Nevertheless, based on two prospective phase II trials (Genentech-sponsored BRAIN-AVF3708g and NCI-sponsored 06-C-0064E trials) with a total of 215 patients and occasional dramatic improvement of symptoms,[33,36] the United States FDA granted accelerated approval for the use of bevacizumab for GBM. In contrast, the European Medicines Agency (EMEA) refused approval for bevacizumab in this setting, arguing that RRs and decrease of contrast-enhancement are not sufficient to demonstrate a reliable antitumour effect in the two uncontrolled phase II studies http://www.ema.europa.eu/docs/en_ GB/document_library/Summary_of_opinion/human/000582/WC500018390.pdf).[28]

Data from well controlled randomised trials on bevacizumab are still not available, but the REGAL study on cediranib supports the notion PFS is not a valid end-point for VEGF inhibitors in trials on brain tumours. Cediranib is a pan-VEGFR tyrosine kinase inhibitor for which similarly high and rapid onset responses were reported in early clinical trials. However, in a subsequent well-designed randomised phase III trial (cediranib alone versus cediranib and lomustine versus placebo and lomustine) no OS benefit was demonstrated in any of the cediranib arms; actually patients randomised to single agent lomustine had the numerically longest survival (median 9.8 months, CI not reported, compared to lomustine + cediranib: 9.4 months or cediranib alone 8.0 months). There was however a clear trend towards improved PFS.

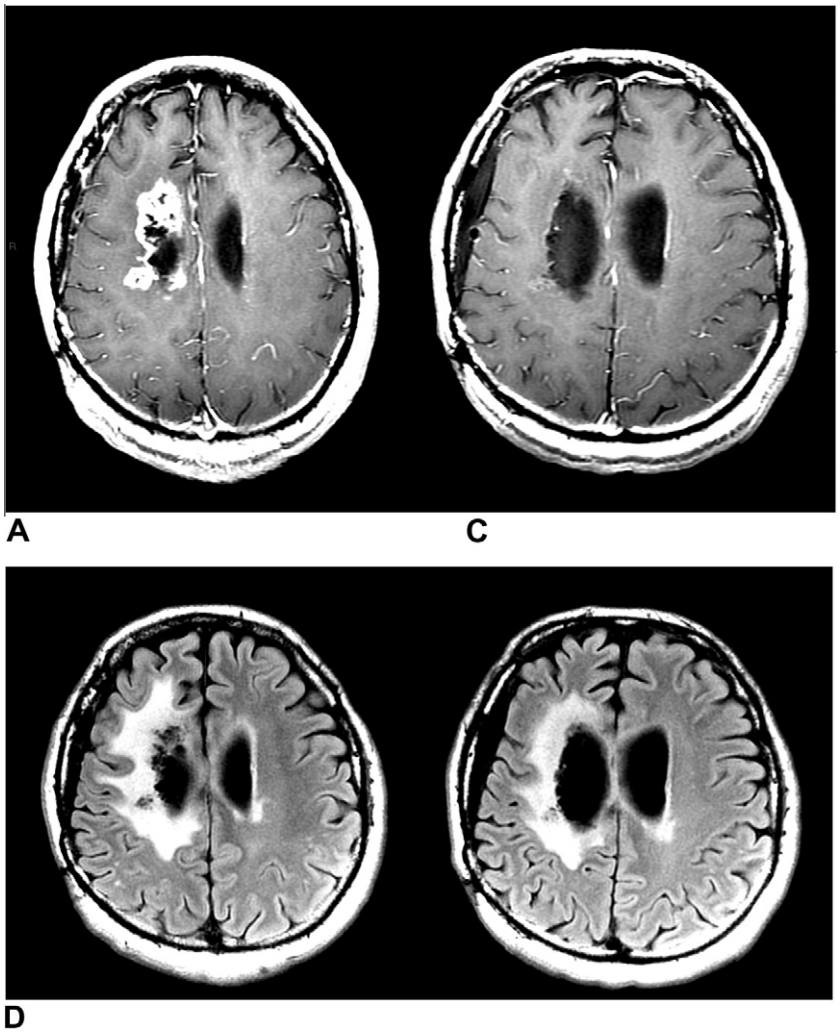

Fig. 1 – A disease response in a glioblastoma patient treated with bevacizumab. (A) baseline contrast-enhanced T1-weighted sequence, (B) baseline FLAIR sequence, (C) contrast-enhanced T1-weighted sequence after 6 cycles of bevacizumab 10 mg/kg every 2 weeks, (D) FLAIR sequence after 6 cycles of bevacizumab 10 mg/kg every 2 weeks.

All trials with VEGF or VEGFR inhibitors showed a decrease in the steroid requirement in the majority of patients and also an at least transient clinical benefit, indicating that these agents may well exert an important biological and clinical effect, whether the real antitumour effect remains to be established.[40] These variable interpretations of data and contradictory conclusions from phase II and phase III trials illustrate the ambiguity of radiological response and PFS as a valid surrogate end-point when antiangiogenic agents are used. Consequently, end-points based on response or progression should be avoided to select the most promising antiangiogenic agents for phase III evaluation, and to avoid futile developments and expose patients to agents with unproved activity (within and outside clinical trials).

There is no general consensus regarding the definition of a valid surrogate end-point for OS, however, a useful surrogate end-point should produce a reliable quantitative estimate of the expected effect of treatment on OS, based on the observed effect of treatment in the surrogate.[41] PFS has failed to be a predictor of outcome and acceptable surrogate for therapies using antiangiogenic agents but also other compounds in neuro-oncology. Interestingly, a similar phenomenon occurs in colorectal cancer where PFS represents a reliable surrogate end-point for patients who undergo cytotoxic chemotherapy. Recent analyses evaluating the predictive value of PFS as a surrogate for OS in patients with metastatic colorectal cancer and other solid tumours treated with chemotherapy and bevacizumab failed to demonstrate a correlation between PFS and OS.[42,43]

In order to address the specificities of clinical trial end-points and surrogate markers in neuro-oncology, a consortium of brain tumour experts convened repeatedly and made some specific recommendations. The Response Assessment criteria in Neuro-Oncology (RANO) working group has developed criteria[2] focusing on overcoming the disadvantages of the classical WHO and Macdonald's response evaluation criteria.[1] These adapted criteria maintain that steroid use and clinical condition need to be considered. In addition, tumour size will be evaluated both on contrast-enhancement and on T2/FLAIR sequences. Just like pseudoprogression with increased contrast leakage after successful therapy has been observed, anti-angiogenic agents may decrease contrast uptake by normalisation of the vasculature without exerting a true antitumour effect, this phenomenon was termed pseudo-response or pseudo-regression. Prospective clinical validation of these new RANO criteria is urgently required in order to evaluate their value and specifically the contribution of T2/FLAIR sequences.[44] Of note, T2 and FLAIR may *per se* also be modified by irradiation, steroid usage, demyelination, ischaemic injury and infection. More importantly, the relative extent of increase of tumour size on T2/FLAIR images to qualify for disease progression, the predictive value of this alteration for a T1-progression or the clinical consequences have not been established yet. Therefore, disease evaluation and, in particular, disease progression assessment remains difficult in patients with recurrence, for whom antiangiogenic approaches are used, and causes a bias in the evaluation of results from clinical trials.

Our ability to evaluate the effects of antiangiogenic therapies on neuroradiological outcomes is, as yet, limited since the use of imaging parameters, notably contrast enhancement does not reflect the true biological changes. Innovative radiological techniques and MR sequences like perfusion and diffusion, spin labelling and vascular permeability and biomarkers such as circulating collagen IV levels or endothelial progenitor cells are being developed for composite scores as markers for early progression.[45,46] Finally, PET with tracers specific for tumour-amino acid transport (MET: [^{11}C]*methyl*-L-methionine or FET: [^{18}F]-fluoro-ethyl-tyrosine) and/or proliferation (FLT: [^{18}F]-fluoro-L-thymidine) have shown some promise.[47–51] The usefulness of these techniques remains to be established though, but the limited access is an obstacle for implementation in most multicentre trials.

7. Conclusions

The heterogeneity of recurrent GBM, a fatal disease with limited survival expectancy even with the use of the best available treatments, warrants exploration of novel treatment approaches and targeting of multiple pathways. The high number of current and proposed treatments that have emerged should lead to a considerable improvement in the prognosis of GBM patients. However, appropriate early assessment of the efficacy of new therapies is crucial, and radiological response may be misleading, especially when anti-VEGF signalling is used. In addition to objective efficacy end-points, trials should also evaluate symptom control and QoL.

It is essential to make a distinction between true clinical efficacy measures (gold standard OS) and indirect measures of biologic activity (e.g. RR, metabolic changes on imaging). For trials evaluating chemotherapy agents PFS-6 is a validated end-point, but when evaluating antiangiogenic agents, PFS remains a weak and highly variable end-point, susceptible to numerous unrelated external factors. Before accepting surrogate end-points in pivotal clinical trials, prospective validation and correlation with survival should be demanded. Plausibility and consistency between surrogate markers and survival outcome is required, e.g. simple prolongation of PFS with subsequent shorter time to death may be a sign of artefactual efficacy, or may indicate induction of resistance mechanisms leading to subsequent more aggressive tumour growth.

The goal of clinical research is not to obtain a statistically significant effect, but rather, as stated by Fleming, 'the primary goal should be to obtain a statistically reliable evaluation regarding whether the experimental intervention is safe and provides clinically meaningful benefit[52]'. Translated to the use of anti-angiogenic agents in neuro-oncology, it is not sufficient to establish a statistically significant effect on a biomarker, such as contrast enhancement variation and steroid use if this is not reflecting reduction of tumour burden and prolongation of survival. Until accurate and validated surrogate end-points are established, OS rates within controlled trials remains the preferred end-point in recurrent glioma treated with antiangiogenic agents.[53]

Conflict of interest statement

	Board membership	Consultancy	Expert testimony	Grants/grants pending	Honoraria for advisory board	Patents (planned, pending or issued)	Payment for development of educational presentations including service on speakers' bureaus	Stock/stock options
Brandes AA	Bristol-Myers Squibb,OncoMethylome Sciences,Roche, Schering-Plough				GlaxoSmithKlineRoche, Schering-Plough			
Franceschi E	No	No	No	No	No	No	No	No
Gorlia T	No	No	No	No	No	No	No	No
Wick W	Roche,MSD,Eli Lilly	No	No	Roche,MSD, Boehringer Ingelheim, Apogenix	No	IDH1 antibody	Roche,MSD	No
Jacobs AH	No	No	No	No	No	No	No	No
Baumert BG	No	No	No	No	No	No	No	No
Van den Bent M	No	Merck Ag,MSD,Eli Lilly, Roche,SienaBiotech, AntisensePharma	No	Roche	No	No	No	No
Weller M	Roche,Merck Serono, MSD	No	No	Roche, Merck Serono	No	No	No	No
Stupp R	No	Actelion	No	MSD (Merck & Co)RocheMerck Serono (EMD)	No	No	MSD (Merck & Co)	No

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