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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

A.A. Brandes [a,*,i], E. Franceschi [a,i], T. Gorlia [b,i], W. Wick [c,i], A.H. Jacobs [d,i], B.G. Baumert [e,i], M. van den Bent [f,i], M. Weller [g,i], R. Stupp [h,i], On behalf of European Organisation for Research and Treatment of Cancer Brain Tumour Group

[a] Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL, Bologna, Italy
[b] EORTC Headquarters, Brussels, Belgium
[c] Department of Neurooncology, Neurology Clinic and National Center for Tumor Diseases, Heidelberg, Germany
[d] European Institute for Molecular Imaging (EIMI) and Department of Nuclear Medicine, Westfalian-Wilhelms University (WWU) of Münster, Germany
[e] Department of Radiation-Oncology (MAASTRO), GROW (School for Oncology & Developmental Biology), Maastricht University Medical Centre (MUMC), The Netherlands
[f] Neuro-Oncology Unit, Daniel den Hoed Cancer Center/Erasmus University Hospital Rotterdam, Rotterdam, The Netherlands
[g] Department of Neurology, University Hospital, Zurich, Switzerland
[h] Department of Neurosurgery, University of Lausanne Hospitals, Lausanne, Switzerland

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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.

* *Corresponding author*: Address: Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL, Via Altura 3, Bologna, Italy. Tel.: +39 0516225102; fax: +39 0516225057.
E-mail address: alba.brandes@yahoo.it (A.A. Brandes).
[i] On behalf of the European Organisation for Research and Treatment of Cancer Brain Tumour Group.
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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-