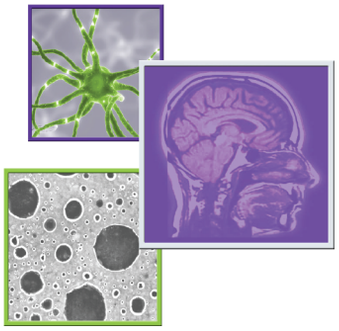
Commentary

CNS Oncology



Imaging and clinical end points in brain metastases trials

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"When designing a clinical trial on brain metastases the choice of end points is critical."

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When designing a clinical trial on brain metastases the choice of end points is critical. The Response Assessment in Neuro-Oncology (RANO) International Group has recently critically reviewed the different end points used in the clinical trials on brain metastases [1,2].

Some factors heavily influence the choice of end points. First, patients with solid tumors may differ in prognosis and competing risk of extracranial progression. Second, the trial setting (Phase II vs Phase III trials) and type of intervention (CNS-directed vs systemic therapies) also require different end points.

The knowledge of prognostic factors, in other words, of those factors influencing the outcome regardless of treatments, is critical in order to identify subgroups of patients with different outcomes (e.g., Recursive Partitioning Analysis [RPA] and Graded Prognostic Assessment [GPA] classes) [3–5]. In clinical trials, these subgroups are essential either as a stratification factor or inclusion criteria or even for *post hoc* analyses.

There are key issues in imaging brain metastases in clinical trials: modalities and frequency of assessment, type and magnitude of change used to define response or progression of disease, and incorporation of steroid use and neurological symptoms/signs with current imaging definitions of response and progression. Last but not least, the ability to differentiate tumor-related and treatment-related changes is another critical point.

The objective response is used to screen the activity of novel compounds and represents a primary end point in Phase II trials. It may be a surrogate for other markers of clinical benefit, such as neurological symptoms, neurocognitive function or survival. The interlesional variability of response to treatment can render problematic the evaluation of response in multiple metastases. A methodological open issue is whether it is preferable a randomized Phase II trial or a single arm Phase II trial with historical control in large datasets (e.g., Radiaition Therapy Oncology Group [RTOG] datasets) when larger Phase III trials are not feasible.

The criteria of response used in brain metastasis trials in the past were quite heterogeneous. The use of MRI for response assessment was not always a standard procedure. There were major areas of difference across trials on brain metastases regarding the evaluation of response to treatment: definition of a target lesion (not defined, $\geq$1 cm); number of lesions (variable); type of measurement (unidimensional, bidimensional, volumetric); degree of tumor shrinkage required for response ($\geq$30%, $\geq$50%); requirement for confirmatory scans (more commonly not required); inclusion of steroids and neurological symptoms (more commonly not done); evaluation of extracranial disease (more commonly not included). Overall, none of the Standard Response Criteria (Response Evaluation Criteria In Solid Tumors [RECIST], WHO, MacDonald and RANO for high-grade gliomas) were designed specifically to evaluate brain metastases, thus investigators have not consistently chosen one set over another, and in some instances have adopted existing criteria in differing ways.

The RANO Group has proposed new response criteria to be validated in the future clinical trials [6]. Basically, the response is based on a unidimensional measurement of the longest diameter of up to five target lesions, with a $\geq$30% decrease to qualify for partial response, taking into account the steroid requirement and the neurological status. Conversely, non-CNS lesions are still measured according to RECIST 1.1 criteria. The existing data are not yet strong to justify the universal requirement of volumetric response criteria in trials on brain metastases, as the

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appropriate cutoff to define a partial response on the basis of volumetric measurement is still a matter of debate. However, the assessment and reporting of volumetric response as a secondary end point in clinical trials (in addition to RANO brain metastasis criteria) are to be encouraged. When employing volumetric criteria for the definition of response, in case a tumor forms a perfect sphere, a 65% volumetric reduction corresponds to a 30% unidimensional reduction. Partial volumetric response should be defined as a 65% or greater decrease in the sum volume of CNS target lesions. Volumetric changes of minimum 20% seem reproducible between readers and clinically meaningful.

Recently, it has been suggested [7] that lowering the minimum diameter of targeted lesions to 5 mm, instead of 10 mm as fixed in the RANO criteria, would significantly increase the number of patients to be accrued in clinical trials.

In trials of patients with metastatic solid tumors outside of the brain, progression-free survival (PFS) is commonly chosen as an end point with the definition of progression according to RECIST 1.1 criteria. In trials of patients with brain metastases, a clear distinction between intracranial PFS, extracranial PFS and overall PFS is needed. However, intracranial PFS has a limited value as primary end point due to several potential caveats deriving from the existence of treatment-related changes. In this regard, there are challenges in the definition of intracranial PFS following local therapies. Transient increase of enhancement on MRI after surgical resection may be of difficult interpretation: thus, routine postoperative MRI (within 72 h from surgery) should be performed to interpret these findings. The differential diagnosis between pseudoprogression/radionecrosis and tumor regrowth after stereotactic radiosurgery is of major importance when using standard MRI. The additive value of advanced neuroimaging techniques, such as MRI spectroscopy, MRI perfusion, PET with amino acids, still needs validation in prospective studies [8,9]. There are challenges in the definition of intracranial PFS following systemic treatments as well. Pseudoresponse after treatment with antiangiogenic agents, especially anti-VEGF compounds such as bevacizumab, consists in a reduction of enhancement and edema on MRI due to a normalization of the vascular permeability, but without an impact on neoangiogenesis and tumor growth. Following immunotherapy, we can observe pseudoprogression, increase in number of lesions and delayed responses: when facing with these findings, in case of a patient still neurologically stable, treatment should be continued [10]. In both instances, close confirmatory MRI scans are requested. Two additional points deserve attention: in trials of local therapies with intracranial PFS as primary end point concurrent and subsequent systemic therapies should be registered and evaluated; in trials of targeted drugs, patients who develop isolated CNS progression but have the extracranial disease under control should be given the option to remain on protocol treatment while CNS-directed treatments (e.g., stereotactic radiosurgery or whole-brain radiation therapy [WBRT]) are added.

Time to deterioration of performance status to WHO more than 2 has been used as a primary end point in EORTC 22952–26001 Phase III trial comparing observation with adjuvant WBRT following either radiosurgery or surgical resection of 1–3 cerebral metastases, and did not differ between the two arms.

Overall survival has been almost universally chosen as primary end point in Phase III trials. It is an unambiguous end point, clinically meaningful (shared by both patients and providers), being survival with functional independence an alternative. The value of overall survival as primary end point is limited by the frequent coexistence of extracranial disease, which may exert a major effect on survival regardless of intracranial disease control and by the influence of salvage treatments. Thus, improved intracranial control may not necessarily translate into improved overall survival. As a matter of fact in the EORTC 22952–26001, about 60% of patients in the observation arm had salvage stereotactic radiosurgery.

The symptom burden, that is collected in case report forms, may vary according to the method of collection and type of physician: there is need for a standardization of the minimum components of a neurological examination and for scoring the individual neurological signs: this was the reason for developing the Neurologic Assessment in Neuro-Oncology (NANO) scale by the RANO Group to be used and validated in future trials. An alternative approach is to rely more heavily on patient reported outcomes, such as the MD Anderson Symptom Inventory Brain Tumor Module. Moreover, there is need to collect prospectively data on seizures.

More than 90% of patients with brain metastases are cognitively impaired at the time of the diagnosis. Cognitive functions predict survival time, and neurocognitive decline occurs before decline in independence and quality of life. Neurocognitive outcomes may serve as a secondary end point to support the clinical benefit of a novel treatment approach (i.e., trials with motexafin gadolinium), while may serve as primary end point when the treatment itself (i.e., WBRT) carries a risk of neurotoxicity [11,12]. Several recent pilot trials have investigated new methods to spare the brain while receiving WBRT by using cognitive functions as primary end point. Memantine, a neuroprotective drug, was investigated in a randomized, double-blind placebo controlled trial [13]. The primary trial end point was

whether the addition of memantine-preserved cognitive function, specifically memory, as measured by the (HVLT)-R for delayed recall Hopkins Verbal Learning Test(HVLT-R DR), compared with placebo at 24 weeks from the start of drug treatment. Secondary end points included time to cognitive failure, overall survival, progression-free survival and assessment of adverse events. Overall, there was less decline in HVLT-R DR in the memantine arm compared with the placebo arm at 24 weeks, but the difference did not reach statistical significance. However, time to cognitive failure was found to have a modest statistical significance favoring the memantine arm.

A Phase II multi-institutional trial evaluating conformal avoidance of the hippocampus during WBRT (RTOG 0933) has been performed [14]. The mean relative decline in HVLT-R DR (primary end point) from baseline to 4 months was 7.0%, significantly lower in comparison with the historical control (30%). Both memantine and hippocampus sparing are now being investigated in a randomized Phase III trial.

A Phase III randomized placebo-controlled clinical trial has investigated the during donepezil to improve cognitive deficits in long-term survivors following WBRT [15]. A cognitive test battery assessing memory, attention, language, visuomotor, verbal fluency and executive functions was administered before random assignment and at 12 and 24 weeks. A cognitive composite score (primary end point) and individual cognitive domains were evaluated. After 24 weeks of treatment, the composite scores did not differ significantly between groups; however, modest significant differences favoring donepezil were observed for memory and motor speed and dexterity.

Heath-related quality of life is a well-established secondary end point in advanced cancer. A number of issues make heath-related quality of life problematic as primary end point in brain metastases trials: of particular importance is the risk of a differential dropout, in other words, patients who have progressed or who experience clinical deterioration are the least likely to complete all of the assessments, thus potentially rendering a treatment more favorable than it really is [16].

There are critical issues when designing trials on targeted agents for established brain metastasis. A first critical issue is that we cannot rely on primary tumor molecular profile, as it has been demonstrated that more than 50% of brain metastasis have divergent molecular pathways in comparison to the primary tumor and/or extracranial metastases [17]. In addition to the presence of the molecular target, the uptake and measurement of drug activity on the molecular target are important, as they can be heterogeneous [18]. Thus, there is need for Phase 0 trials, in which the molecular drug to be investigated is administered before surgery allowing a measurement of drug distribution and activity in the surgical specimens.

Regarding the issue of leptomeningeal metastases in trials on brain metastases two main points are relevant. First, the risk of leptomeningeal relapse after local treatments (resection and/or stereotactic radio-surgery and/or WBRT) must be prospectively investigated. Second, a coexistence of leptomeningeal metastases with brain metastases at diagnosis is detected in up to 50% of patients: both can be included in trials with molecular drugs, but responses must be evaluated separately in the two compartments.

For designing clinical trials on prevention of brain metastases there are three prerequisites, in other words, the ability of a promising agent to adequately cross a normal blood–brain barrier, the identification of subgroups of patients at high risk of CNS relapse, and the use of specific end points, such as incidence of brain metastases (at 1 or 2 years, cumulative) and/or intracranial PFS [19]. In this regard, the usefulness of surveillance with MRI in subgroups of patients with high risk of relapse in the brain, such as HER 2+ breast cancer patients, is now recognized [20].

In conclusion, trials of new systemic-targeted treatments should be limited to a specific primary tumor type and/or molecular subtype. Trials of surgery, radiosurgery or WBRT can accrue patients with mixed tumor histologies, but in case of randomized trials a stratification of the patient population is needed. The new proposed RANO criteria must be validated within future clinical trials. Neurocognitive and quality of life end points should always be used.

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