EDITORIAL

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Inclusion of patients with brain metastases in clinical trials

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A major goal of oncology drug development is the discovery of new agents to effectively treat patients with locally advanced or metastatic tumor. Clinical trials largely target patients with widespread tumor who have failed standard therapy and are no longer eligible for local therapy. Although the brain is one of the most common sites of solid tumor metastases, patients with brain metastases are routinely excluded from clinical trials testing new, investigational anticancer agents. Multiple rationales have been used to justify this specific exclusion criteria; poor prognosis, lack of blood–brain barrier penetration and unacceptable risk of CNS hemorrhage or toxicity are the most frequently cited. However, it is increasingly clear that many of the clinical assumptions related to brain metastases have evolved and changed in a way that mandates reassessment of these preconceived notions.

Changing paradigms

The standard of care for a patient with newly diagnosed brain metastases has been carefully worked out over the past several decades by a series of trials investigating neurosurgical and radiotherapeutic approaches [1]. However, the reality for most patients is that at some point after the initial CNS-focused treatment either their CNS or systemic tumor will progress and additional therapy will be required. It is also likely that standard systemic treatments used for the underlying primary malignancy will have already been exhausted, leaving participation in a clinical trial as the preferred or recommended standard of care.

Historically brain metastases were diagnosed in the setting of end-stage malignancy; 70% or more of patients would have concomitant active lung metastases and expected survival at diagnosis of brain metastasis was on the order of 3–4 months [2]. For a variety of reasons this clinical paradigm has shifted for many patients. Advances in imaging techniques, availability and widespread usage have led to many patients being diagnosed early with brain metastasis in the absence of significant CNS symptomatology. In addition, many patients are now diagnosed with brain metastases in the setting of controlled systemic disease. Improvements in systemic therapy resulting in prolonged systemic tumor control may increase the overall risk for developing brain metastasis. Prolonged survival also allows a longer interval for brain metastases to develop. Furthermore, some drugs with poor blood-brain barrier penetration, such as trastuzumab, might be adequate to control systemic disease, but inadequate to prevent the growth of microscopic metastatic deposits residing behind the blood-brain barrier [3]. Regardless, there is clearly a subset of brain metastasis patients who are in better than expected clinical condition and these patients may be well enough to participate in, and benefit from, investigational therapies.

Keywords: blood-brain barrier • brain metastases • cerebral hemorrhage • chemotherapy • clinical trials



The blood-brain barrier is another frequently cited reason as a rationale for excluding brain metastasis patients from clinical trial participation. However, this rationale is clearly flawed. While many novel agents may fail to penetrate the blood-brain barrier, this is largely an issue for the prevention of brain metastasis. Once a brain metastasis has grown beyond approximately 0.2 mm it acquires a neovasculature that is not behind the privileged blood-brain barrier [4]. The simplest evidence for this is the visualization of brain metastases following administration of gadolinium contrast on MRI. More detailed modeling has shown that the vasculature of brain metastases lacks the anatomic and physiologic features that characterize a functional blood-brain barrier [5]. However, the vasculature of a brain metastasis is similar to other visceral metastases with abnormal flow patterns, increased interstitial fluid pressure and therefore optimizing drug delivery strategies is crucial to the treatment of all metastases.

Finally, a frequently cited concern regarding the enrolment of patients with brain metastasis on clinical trials is the increased risk of CNS toxicity. In particular, the risk of CNS hemorrhage is often considered to be unacceptable and concerns are often raised about other possible CNS complications, such as seizure or encephalopathy. While CNS symptoms are often the presenting sign of a brain metastasis, it is possible to adequately treat these symptoms in most patients with appropriate medications or definitive therapy. CNS hemorrhage is an uncommon complication of brain metastases that varies somewhat by histology with estimates of 1-2% [2,6]. Assessment of CNS toxicity rates among brain metastasis patients receiving new agents will be critical to determine if excess toxicity is a real concern or a misconception.

What happens when brain metastasis patients participate in clinical trials?

In spite of these concerns there is an increasing amount of data available regarding the feasibility of patients with brain metastasis participating in clinical trials.

A number of clinical trials have been conducted to specifically look at drug therapies, both traditional cytotoxic agents as well as targeted molecular agents, for patients with recurrent or newly diagnosed brain metastases [7-10]. The value of these studies is that they demonstrate objective response rates in brain metastases that are often similar to that seen in other metastatic sites; most have also confirmed the expected pattern of drug-related toxicity without increased CNS-specific toxicity. In particular, recent studies of BRAF inhibitors in patients with malignant melanoma and brain metastases show an excellent response rate in the brain, without an increase in CNS toxicity or CNS hemorrhage [10]. The major limitation of specific trials for brain metastasis is that brain metastases rarely occur in isolation. Enrolment, endpoints and selected treatment requirements have often failed to address issues related to active systemic disease or the need to continue effective treatments that are controlling underlying systemic tumor.

Evidence is also available from a number of trials designed for patients with stage 4 malignancy that permitted enrolment of patients with brain metastases. This data is often heterogeneous but allows some preliminary observations on the impact of including brain metastases patients on clinical trials.

The MD Anderson Cancer Center Phase I group reviewed their experience in enrolling patients with brain metastases on Phase I clinical trials [11]. Although this comprised less than 10% of all patients enrolled on Phase I trials, several valuable findings were reported. Time to treatment failure, arguably the most critical variable in a Phase I study, was identical in patients with or without brain metastases. This is crucial because the goal of most Phase I studies is the assessment of dose and toxicity in the first one to two cycles of drug delivery. Furthermore, the rates of grade 3 and 4 toxicity were not statistically different for patients harboring a brain metastasis as compared with other trial participants (12 vs 10%). There was no evidence of excess or unique CNS toxicity among participants with brain metastases. Finally, the presence of brain metastases was not a predictor of survival on multivariate analysis. Similar data has been reported from the Royal Marsden group [12]. Taken together, this data suggests that including patients with brain metastases does not compromise the conduct or outcome of Phase I trials [13-15]

An analysis of a large Phase III trial in non-small-cell lung cancer, which allowed patients with treated brain metastases to participate, found that rates of clinical benefit were similar in the subgroup containing brain metastases as compared with no brain metastases [16]. Clinical outcome measures included response rate, overall survival and time to progression. Overall toxicity was similar between the two groups although there was a slight increase in selected toxicity such as nausea in the brain metastasis population.

CNS hemorrhage is a particularly feared treatment-related complication, as a result, patients with brain metastases were excluded from most early trials of VEGF inhibitors after an early CNS bleed was reported in a study patient with hepatocellular carcinoma. Despite this perceived risk, a number of patients with brain metastases were enrolled in trials of VEGF inhibitors such as bevacizumab and sunitinib. Among nearly 14,000 patients, 543 brain metastases patients were treated with bevacizumab and there was no evidence to suggest an increased risk in the rate of CNS hemorrhage of any grade [17]. Similar data also exists for patients with renal cell carcinoma and brain metastasis treated with sunitinib [18]. In addition, a specific trial looking at the efficacy and toxicity of sunitinib in non-small cell lung cancer patients with recurrent brain metastases found no evidence of CNS hemorrhage on central radiographic review [8].

Future perspective

The current trend is to allow patients with treated or controlled brain metastases to participate in some clinical trials. While this is a step in the right direction, it leaves several problems. First there is no standard definition of treated or controlled brain metastases. While it seems reasonable to verify that a patient has received the standard of care prior to being offered experimental therapy, the very reason that most patients seek participation in a clinical trial is that they have already failed standard therapy. Patients with progressive brain metastases alone or in concert with systemic progression may be appropriate candidates for novel therapies.

The science necessary to understand the molecular and genetic features driving metastatic patterns is rapidly evolving. The molecular and genetic features that cause certain metastatic cells to home to the brain and other visceral sites may also harbor a phenotype that is inherently resistant to certain types of therapy but may also be sensitive to novel targeted therapies [19]. Inclusion of brain metastases patients in trials of new agents will be critical to assess therapeutic potential [20].

Recent refinements in prognostic scores allow us to differentiate brain metastasis patients with adequate potential survival to meet inclusion criteria for most clinical trials [15,21-23]. Therefore, it seems reasonable in general to offer patients with brain metastases to participate in appropriate clinical trials similar to patients with other visceral metastases. Clearly trials targeting a specific metastatic site or paradigm should remain limited, but otherwise inclusion and exclusion criteria should stipulate critical issues related to trial design and feasibility rather than simply excluding brain metastases. The available data suggests that patients with brain metastases have the potential to benefit from new therapies, do not experience a different pattern of toxicity and, provided that other eligibility criteria are fulfilled, do not undermine the conduct or results of new drug trials.

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