Inclusion of Patients with Brain Metastases in Phase I Trials: An Unmet Need

Mrinal M. Gounder and David R. Spriggs

Patients with brain metastases are increasing in number; however, these patients are often excluded in phase I/II trials due to perceived poor prognosis, risk of hemorrhage, inefficient drug delivery, and confounding toxicities. Tsimberidou and colleagues demonstrate that selected patients can be appropriately enrolled in phase I trials and have outcomes representative of the general cancer population.

In this issue of *Clinical Cancer Research*, Tsimberidou and colleagues (1) report their single-institution experience of patients with brain metastases treated in various phase I clinical trials. This series reports on a neglected topic in experimental oncology and follows on the heels of an abstract detailing the Royal Marsden Hospital experience (2) and an excellent editorial (3). More than 170,000 patients with brain metastases are identified annually, and treatment of such patients poses a significant clinical challenge due to the confined anatomic location of the tumors, the blood-brain barrier (BBB), and variant tumor biology (4).

The goal of phase I studies is to establish the safety, dose, toxicity, and pharmacokinetics of a new drug or regimen (5). In identifying appropriate patients, clinicians must weigh on one hand the scientific and clinical benefits, and on the other hand the risk of delay from unrelated toxicity and early patient drop-out. A meta-analysis of phase I trials showed overall response rates, stable disease, and toxicity-related deaths of approximately 10%, 34%, and 0.5%, respectively (6). Although these are surrogate endpoints, in selected patients (e.g., those with EGFR\textsuperscript{mut} non–small cell lung cancer) this can be used to predict a survival benefit. Eligibility criteria serve as objective guidelines to identify low-risk, appropriate patients, and typically exclude patients with poor performance status, organ dysfunction, a life expectancy of <12 weeks, concomitant medications that interfere with metabolism, and comorbidities (e.g., brain metastases).

Brain Metastases and Clinical Trials

Patients with brain metastases represent a heterogeneous population with a wide range of outcomes. Gaspar and colleagues (7) retrospectively analyzed 1,200 patients with brain metastases who presented with neurological symptoms and were enrolled in Radiation Therapy Oncology Group randomized trials from 1979 to 1993. The authors evaluated various radiation doses, schedules, and radiosensitizers, and on the basis of a recursive partitioning analysis proposed 3 prognostic classes. Class I patients had a Karnofsky performance status (KPS) greater than 70, age under 65 years, controlled primary disease with brain-only metastatic site, and a median overall survival of 7.1 months. Class III patients had a KPS less than 70 and survival of 2.1 months. Class II patients had a survival of 4.5 months and were neither class I nor class III. To further refine the model, other investigators have used prognostic indices incorporating age, control of primary disease, response to steroids, number and volume of brain metastases, and/or time to develop lesions (8). We now know that smaller tumors (<0.2 mm) generally maintain an intact BBB, whereas larger, “imageable” lesions have a tumor neovasculature that is often under the influence of vascular growth factors such as VEGF, which is permeable and lacks the p-glycoprotein expression typical of normal brain vessels (9, 10). In a recent study, a murine brain metastasis model showed tumor–brain-barrier disruption that was independent of tumor size [0.3–3 mm\textsuperscript{2}] (ref. 11)]. There are no prognostic indices or optimal management strategies for low-risk, asymptomatic patients whose tumors may be discovered incidentally. Although small studies in non–small cell lung cancer and breast cancer suggested that early and delayed radiation therapy (RT) produced similar outcomes (12), most investigators would favor prior brain metastasis treatment before entering a patient into a clinical study. The optimal duration between surgery/radiation and systemic therapy remains unclear and has been arbitrarily set at 1 to 6 months.
Furthermore, steroids, antiepileptics, and anticoagulants may complicate the pharmacokinetics and thus are generally excluded.

The MD Anderson Cancer Center Experience

In the study presented in this issue, Tsimberadou and colleagues (1) evaluated 1,181 patients enrolled in various phase I trials and compared them with a subset of 93 patients with brain metastases in terms of outcomes. The latter group constituted 8% of the entire cohort and had a median age of 54 years, a higher percentage of women (61%), lower liver metastases, and central nervous system (CNS) disease that was nonhemorrhagic, treated, and stable for 3–6 months. Approximately 88% of the patients were previously treated with CNS-RT, and the remaining patients had refused radiation (6 points) or were asymptomatic (4 points). The size or volume of the lesions and the distribution of patients with active or recurrent CNS disease are not reported. From the time of initial diagnosis, CNS-RT was started and completed within a median of 0.7 and 5.5 months, respectively. Patients were enrolled in a trial within a median of 10.2 months from CNS diagnosis. Brain metastasis was more likely to be treated with targeted agents (85% vs. 65%) than with combinations (6% vs. 23%). We suspect this bias is related to common misperceptions among patients and physicians that targeted agents are less toxic and more efficacious than cytotoxics. However, the treatment modality did not affect the time-to-treatment-failure (TTF) or overall survival. The study reports no differences in grade 3/4 toxicities between the 2 cohorts. When restricted to patients treated with the same protocols, there was little difference (4.3% vs. 2.3%) in grade 3/4 peripheral neuropathy, confusion, or seizures. Concurrent use of steroids, anticonvulsants, and/or anticoagulants is not reported. Patients with and without brain metastases showed the following responses: overall response rate = 2% and 5%, stable disease >4 months = 15% and 22%, and progression of disease = 83% and 73%, respectively. A multivariate analysis showed that no prior CNS-RT and normal lactate dehydrogenase predicted for survival, likely reflecting indolent biology. It can be difficult to obtain a radiographic measurement of response in brain metastases. In high-grade glioma, the McDonald criteria and other...
measures are used to counter antiangiogenic effects, steroid use, radiation necrosis, and nonenhancing lesions. Whether these criteria should be applied to evaluate brain metastases remains unexplored. Patients with brain metastases had a shorter duration of survival than those without brain metastases (7.5 vs. 10.3 months), and this difference was also seen in patients treated with the same protocols (7.5 vs. 9.8 months). Factors predicting for poor survival were performance status, number of prior therapies, liver metastases, thrombocytosis, and hypoalbuminemia. A key finding is the similar median TTF for the patients with brain metastases. For phase I studies, the percentage of patients who are evaluable after 1 to 2 cycles may be a more important endpoint than the median TTF.

Conclusions

In their study, Tsimberidou and colleagues show that carefully selected patients with good performance status can be safely enrolled in clinical trials without risk to the patient or damage to the trial. Patient benefit, time in study, and toxicities appear to be similar in an unselected phase I population and patients with brain metastases. An important limitation of the study is a significant selection bias for patients referred to and subsequently enrolled in phase I trials. We do not know the overall percentage of all patients with brain metastases who entered these phase I studies, so it is difficult to generalize the results to unselected patients with brain metastases. It is also unclear how established brain metastasis prognostic factors for survival and response should be used to guide the phase I entry decision. Currently, no guidelines exist for stratifying and evaluating patients with brain metastases in phase I trials. In Fig. 1 we build on a previously proposed algorithm for considering enrollment of patients with brain metastases in phase I trials (3). Patients presenting with neurologic symptoms; hemorrhagic, multiple, or large lesions; and involvement of a critical area must be evaluated for definitive or palliative therapy. If they have been neurologically stable for 1 to 3 months, they may be considered for phase I clinical trials if they meet the eligibility requirements. If there is no evidence of disease (brain or systemic) after intervention, then adjuvant trials evaluating vaccine, immunotherapy, or microenvironment targets may be considered. Patients with low-volume, asymptomatic disease may be considered for phase I trials, with local therapy offered early or later. Decisions should be made by a multidisciplinary board involving medical, neurology, radiation, and surgical specialties. The possible inclusion of patients with brain metastases in early clinical trials should reflect the heterogeneity of this population, but success will ultimately depend on the experience and good judgment of the investigators.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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