It Is Time to Include Patients With Brain Tumors in Phase I Trials in Oncology

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Traditionally, the majority of phase I studies of novel agents in oncology have excluded patients with primary brain tumors. Although phase I studies are designed to determine optimal dosing, efficacy data are increasingly used to look for a signal in particular tumors. Excluding patients with primary brain tumors from phase I studies results in a significant handicap in the identification of drugs that may be particularly active in these tumor types. In this era of targeted therapies, we suggest that the reasons for excluding these patients are largely obsolete. It is time to reconsider this practice and include patients with brain tumors in phase I trials in oncology.

Several reasons are given for the exclusion of patients with brain tumors from phase I trials. First, patients with brain tumors were historically treated with cytochrome P450 enzyme-inducing antiepileptic drugs (EIAEDs), such as phenytoin and carbamazepine, which potentially accelerated hepatic metabolism of the agent under study. As a result, a separate phase I study was often required for patients with brain tumors who were receiving EIAEDs, and the required dose to achieve the same exposure as that of patients not receiving an EIAED was often two- to three-fold higher.1-3 Second, patients with brain tumors were perceived to be in poor condition with a short life expectancy and therefore likely to add to the potential adverse events associated with the study drug, and unlikely to remain stable for a sufficient length of time to allow toxicities to be evaluated during the required period. Third, patients with primary brain tumors were thought to be at increased risk for particular toxicities such as hemorrhage. Fourth, neurologic symptoms and signs from the tumor were believed to be difficult to separate from drug-related neurotoxicity. Fifth, the passage of many agents across the blood-brain barrier (BBB) was uncertain. Another unspoken reason is that some medical oncologists are uncomfortable caring for patients with primary brain tumors, who are usually treated by neuro-oncologists.

However, most of the reasons for excluding patients with brain tumors from phase I trials are no longer valid. Few patients with brain tumors are now treated with traditional EIAEDs. Antiepileptic drugs are not recommended, and the majority of patients who require antiepileptic drugs are treated with non-EIAEDs such as levetiracetam, pregabalin, lamotrigine, topiramate, and lacosamide. Currently, brain tumor trials routinely exclude patients who are receiving EIAEDs if the drug under investigation is metabolized by the cytochrome P450 system; this does not seem to affect accrual. There is no longer a need for separate phase I studies in patients with brain tumors; the maximum-tolerated dose determined in phase I trials for systemic cancers is also the maximum-tolerated dose for brain tumors. The frequent use of corticosteroids in patients with brain tumors is sometimes used as an argument against including these patients in phase I trials, but the effect of corticosteroids on drug exposure is minimal.

The condition of patients with brain tumors is usually no worse than that of patients with systemic cancer. Patients with brain tumors are often relatively young (median age of patients in glioblastoma trials is about 55 years) and have few systemic comorbidities. They tend to have had relatively few prior treatments with systemic agents and there are no systemic metastases, so organ function is generally good and often better than that of patients with systemic cancer who enter phase I trials. Patients with glioblastoma who have recurrent disease and reasonable performance status usually have a life expectancy of 4 to 7 months,4,5 which is
comparable to or better than the expected survival of patients with other solid tumors who have exhausted standard treatment options, and the vast majority of patients with glioblastoma are able to remain on study long enough for drug toxicity to be evaluated adequately.

Multiple phase I trials conducted exclusively in patients with brain tumors failed to demonstrate an increased risk of CNS hemorrhage, including those that evaluated bevacizumab and other antiangiogenic agents; in these studies, the risk of hemorrhage proved to be modest.6-8 Differentiating drug-related neurotoxicity from the effects of the tumor is similar to separating drug toxicity effects on other organs from the effects of systemic metastases. In reality, differentiating tumor-related neurologic symptoms from potential drug toxicity is straightforward and rarely causes confusion.

The drug’s ability to pass through the BBB is an area of valid concern. Although the center of most high-grade primary brain tumors often has a disrupted BBB, the ability of a drug to reach peripher al areas of the tumor where the BBB is relatively intact is also important for it to achieve a therapeutic benefit. Drug structure, molecular weight, lipophilicity, potential impact of drug efflux pumps, and preclinical biodistribution studies should provide some guidance as to whether a drug can cross the BBB. If there is evidence that the drug can pass through the BBB, there is no reason to exclude patients with primary brain tumors from the phase I study. Conversely, if preclinical studies suggest that drug penetration may be limited, it may be reasonable to consider excluding patients with brain tumors from the phase I study. However, even this situation is complex. Agents that target the tumor stroma or vasculature may not need to pass through the BBB to be effective. In addition, there are examples of large antibodies, such as rituximab in primary CNS lymphoma9 and bevacizumab in glioblastoma,6,7 with which therapeutic effects were seen despite concerns about the ability of these agents to pass through the BBB.

In this era of targeted therapy, we hope to include all tumors in phase I studies on the basis of the presence of the correct molecular target, rather than having protocols routinely exclude patients with primary brain tumors. For instance, because the phosphatidylinositol 3’-kinase (P13 kinase) pathway is activated in the majority of patients with glioblastoma (15% have PIK3CA or PIK3R1 mutations and 40% to 50% have loss or mutation of phosphatase and tensin homolog deleted on chromosome 10),10 it would be advantageous to include glioblastomas in trials of PI3 kinase inhibitors if those inhibitors have reasonable access across the BBB. Excluding patients with brain tumors will slow our ability to find better treatments for these patients for whom so few effective therapies exist, and potentially means a lost opportunity to identify a responsive tumor type. Temozolomide is one of the few drugs that is approved for high-grade gliomas, and inclusion of patients with brain tumors into the phase I trial determined the fate of this important agent.11 Activity was seen in patients with high-grade gliomas, and eventually the drug received approval from the US Food and Drug Administration for both recurrent anaplastic gliomas and newly diagnosed glioblastoma. If this drug had been evaluated only in systemic cancers, it is unlikely that its activity against primary brain tumors would have been identified, and as a result, one of the few outcome-changing drugs in glioma treatment would not have become an option for our patients.

The inclusion of patients with primary brain tumors in phase I studies may increase the complexity of those studies, given that the response criteria for systemic tumors12 and primary brain tumors13 are different. However, the added complexity is relatively modest. Recently, medical oncologists conducting phase I studies and neurooncologists at a limited number of centers have been working together to include patients with brain tumors in protocols when a strong scientific rationale exists. Unfortunately, at most centers, this does not occur. It would be of benefit to both patients and pharmaceutical companies to include patients with primary brain tumors in the majority of phase I trials in oncology.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Minesh P. Mehta, Pharmacyclics (C); Consultant or Advisory Role: Timothy F. Cloughesy, Roche (C); Tracy T. Batchelor, Roche (C), Amergin (C), Merck (C); Bruce A. Chabner, sanofi-aventis (C), Allergan (C), Epizyme (C), PharmMar (C), GlaxoSmithKline (C), Peregrine Pharmaceuticals (C), Onyx Pharmaceuticals (C); John F. de Groot, Genentech (C); Minesh P. Mehta, Merck (C), TomoTherapy (C); W.K. Alfred Yung, Merck (C), Novartis (C), Edens (C); Stuart A. Grossman, Merck (C), Roche (C), Diffusion Pharmaceuticals (C), Tau Pharmaceuticals (C), Medimmune (C); Stock Ownership: Bruce A. Chabner, PharmaMar, Gilead, Epizyme, Human Genome Sciences, Onyx Pharmaceuticals, Erexlix, Merck, Rigl Pharmaceuticals, Seattle Genetics; Minesh P. Mehta, Pharmacyclics, TomoTherapy; Honoraria: Timothy F. Cloughesy, Genentech, Roche, AstraZeneca, Agios, Eli Lilly; Bruce A. Chabner, Eli Lilly; Minesh P. Mehta, Merck; W.K. Alfred Yung, Merck, Novartis, Edens; Research Funding: Tracy T. Batchelor, Pfizer, AstraZeneca, Millennium; John F. de Groot, AstraZenea, Adnexus; Susan M. Chang, Novartis, Schering-Plough; W.K. Alfred Yung, Novartis, Daiichi

EXPERT TESTIMONY: None

Remuneration: None

A UTHOR CONTRIBUTIONS
Administrative support: Patrick Y. Wen
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

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DOI: 10.1200/JCO.2011.36.6328; published online ahead of print at www.jco.org on July 18, 2011