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Competing interests
The author declares no competing interests.

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MEDICAL ONCOLOGY

Patients with brain metastases in early-phase trials

Nicholas F. Marko and Robert J. Weil

A recent publication presented objective evidence that patients with and without brain metastases perform similarly in phase I clinical trials for advanced-stage cancer. This finding supports what neurosurgeons and neuro-oncologists have long suspected; namely, that the presence of brain metastases need not mandate exclusion of patients from early-phase clinical trials.

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Brain metastases (BM) occur in 10–15% of patients with advanced-stage, systemic malignancies.[1,2] Traditionally considered a poor prognostic feature, historical studies demonstrated average survival times of 2 months when patients with BM were managed with corticosteroids alone[3] and 3–7 months with the addition of whole-brain radiation therapy (WBRT).[4] The addition of aggressive surgical resection to WBRT has also improved survival by several months and, more importantly, improved local control of central nervous system (CNS) disease such that systemic progression became the primary cause of death in the majority (84%) of patients.[5] Modern multimodality therapy, including combinations of surgery, WBRT, and stereotactic radiosurgery, has improved the overall mean survival time of patients with BM to 3–18 months and has shifted the principal determinant of survival to the status of the primary disease in the majority of patients.[2,6] Indeed, survival in select patients with aggressively managed, asymptomatic BM now exceeds 21 months.[7]

Practice point

Modern multimodality therapy for brain metastases has improved overall survival and helped to equalize the time-to-treatment failure between patients with and without brain metastases participating in phase I clinical trials; therefore, the presence of brain metastases should no longer *de facto* exclude patient enrollment in early-phase clinical trials.

The historically poor prognosis of patients with BM has resulted in their exclusion from many early-phase clinical trials.[8] Unfortunately, this trend has persisted despite the aforementioned improvements in CNS control and overall survival of patients with BM. Therefore, these patients continue to be excluded from most early-phase clinical trials that may offer clinical benefit to the patients and generate valuable data to further improve clinical outcomes. To estimate the magnitude of this effect, we searched the NIH clinical trials database[9] for interventional, phase I trials recruiting patients with lung cancer. Of 234 active protocols, 115 (49%) excluded at least some patients with BM. Of these, 83 studies (35% of the total) limited enrollment of patients with BM described as 'active', 'symptomatic', or 'uncontrolled': terms that have not been defined by a general consensus of neuro-oncologists. The other 32 studies (14% of the total) categorically excluded patients with any history of BM, regardless of the present extent of CNS disease or the treatment history of the brain lesions (Figure 1). These statistics are comparable with those of patients enrolled in the phase I clinical trials program at the MD Anderson Cancer Center, where 43% of the trials excluded at least some patients with BM.[8]

While the exclusion of patients with BM from early-phase trials might occasionally be warranted based on the specific objectives or therapeutic modalities of a particular trial, many neurosurgeons and neuro-oncologists believe that this degree of therapeutic nihilism towards patients with BM is inappropriate given the advances in CNS control and overall survival of patients with metastatic cancer. A recent study by Tsimberidou *et al.*[8] presents the first objective data to support this contention. In 1,181 patients treated in the MD Anderson Cancer Center's phase I clinical trials program, they observed no significant difference in time-to-treatment failure (1.74 months versus 1.84 months; $P = 0.61$) or in the frequency of grade 3 or 4 toxic effects (12% versus 10%; $P = 0.77$) between patients with and without BM. Moreover, on multivariate analysis, the presence of BM was not an independent factor predicting overall survival (7.5 months, 95% CI 6.1–10.3 months versus 10.3 months, 95% CI 9.4–11.3 months; hazard ratio 1.21,

$P = 0.22$). The investigators concluded that, given "the grave nature of brain metastases and the urgent need to find new treatments for them … enrolling patients with brain metastases on early clinical trials is safe and should be encouraged".[8]

We agree with the assessment of Tsimberidou *et al.*[8] that there is an urgent need to find new treatments for patients with BM, and we echo their sentiments that the presence of BM should not result in *de facto* exclusion of patients from phase I trials that might otherwise afford the chance of clinical benefit for advanced-stage cancer. The frequently held conception that the presence of BM portends imminent neurologic decline and impending death are predicated on outdated data. While WBRT and corticosteroid therapy was once the sole, palliative treatment strategy for patients with BM,[3] the rapidly evolving, modern era of multimodality management of CNS disease has afforded a nearly fourfold increase in the mean survival expectation of these patients over the past 15 years.[2,6] Aggressive local therapy for BM has shifted the nature of morbidity and death of these patients, with the majority of those with advanced-stage cancer now dying from their primary disease rather than from their CNS metastases.[2,6] These findings, combined with those of Tsimberidou *et al.*,[8] strongly support the inclusion of patients with BM in phase I clinical trials.

Although the analysis of Tsimberidou and co-workers focuses exclusively on patients participating in phase I trials,[8] we believe that their data can readily be generalized to another category of early-phase clinical trial that may be of particular value in the population of patients with BM, the 'phase 0' trial.[10] This emerging, 'target-development clinical trial' paradigm focuses on extensive agent characterization and target-assay development in a limited number of patients and is designed to inform and to expedite the development of molecularly targeted agents.[10] Conducted under the Exploratory Investigational New Drug Application of the FDA's Critical Pathway Initiative and designed to determine the 'biologically effective dose' rather than the maximum-tolerated dose (as in phase I trials), these

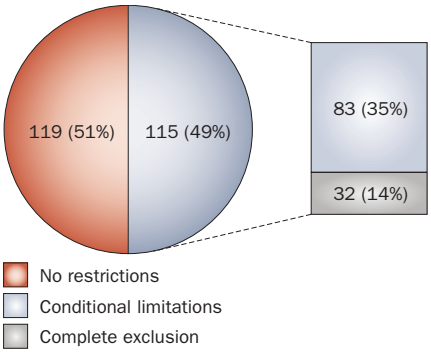

Figure 1 | Enrollment of patients with BM in phase I clinical trials for lung cancer. The clinicaltrials.gov repository[9] was searched for interventional, phase I trials that are currently recruiting patients with lung cancer. Of 234 active protocols, 115 excluded at least some patients with BM (83 trials limited enrollment of patients with BM described as 'active', 'symptomatic', or 'uncontrolled' and 32 studies categorically excluded patients with any history of BM). Abbreviation: BM, brain metastases.

first-in-human trials, "provide data on which to base informed decisions about further clinical development of a specific agent, as well as the design and execution of phase I–II trials".[10] Accelerated development of molecularly-targeted anticancer agents may be of particular value in patients with BM, where challenges in drug delivery and narrow therapeutic indices limit the value of nonspecific, cytotoxic chemotherapeutics. Accordingly, it is critical that patients with BM be included in early-phase trials, and we believe that the finding of Tsimberidou *et al.*[8] provides valuable evidence to support this practice.

In summary, modern, multimodality therapy for patients with BM has resulted in significant improvements in local control and overall survival, and CNS disease is no longer the primary determinant of premature debility or mortality.[2,6] Based on modern outcomes data (including the findings of Tsimberidou *et al.*[8]) we recommend that investigators abandon the practice of *de facto* exclusion of patients with BM from early-phase clinical trials and extend the potential benefits of phase 0 and phase I clinical trials to this patient population.

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