Neuro-oncology clinical trials: Promise and pitfalls

The treatment of malignant neoplasms involving the central nervous system, from either primary or metastatic cancer, remains inadequate. Despite intensive efforts in laboratory and clinical investigations, the prognosis for patients with involvement of the central nervous system remains grim. For example, patients with glioblastoma multiforme have a median survival of less than one year, similar to that reported in 1980 [1]. Similarly, patients with metastatic lesions from systemic cancer continue to do poorly unless the lesions are few in number (3 or less) and are amenable to both local (surgical removal or radiosurgery) and whole brain radiotherapy [2]. Clearly, significant advances are needed in the treatment of malignant brain tumors.

There has been great interest in developing chemotherapy-based treatment strategies for brain tumors, focusing mainly on primary glial neoplasms (i.e., anaplastic astrocytoma and glioblastoma multiforme). Early investigations into the biology of these tumors recognized that the lesions are extremely heterogeneous. These tumors form a solid distinct mass that is easily visible using current imaging modalities. However, pathologic evaluations reveal significant infiltration of the surrounding brain parenchyma by tumor cells, detectable only by microscopic examination [3]. Imaging studies of this area, often referred to a 'brain-around-tumor' (BAT), show either edema or normal appearing parenchyma. Conversely, brain metastases usually exhibit clear delineation between tumor and surrounding normal brain. Malignant brain tumors, both primary and metastatic, are typically enhancing on imaging studies, indicating blood–brain barrier dysfunction in the region. The enhancing region encompasses the entire metastases, but glial neoplasms have a non-enhancing, infiltrating component present in the surrounding brain parenchyma, in which the blood–brain barrier remains functional.

Therefore, despite pathologic differences in regional infiltration of tumor, patients with infiltrating glial malignancies, and those with multiple brain metastases, have a common need for a treatment that encompasses a large portion of the brain. For this reason, external beam radiotherapy is the standard treatment for both types of central nervous system cancers. Although proven to be efficacious, radiation therapy is not curative and recurrent tumor is a frequent occurrence, which has elicited great interest in developing chemotherapy strategies for recurrent cancers. Three manuscripts in this journal describe studies using the chemotherapy agent, temozolomide, for recurrent malignant gliomas and recurrent brain metastases [4-6]. This enthusiasm stems from several factors: temozolomide is an oral agent; has a low incidence of side-effects, non-cumulative myelotoxicity; and crosses the blood–brain barrier [7]. Additionally, pharmacokinetic studies indicate that the metabolism of temozolomide is not altered by concurrently administered drugs that modify the hepatic cytochrome p450 system, including many of the anticonvulsants, a problem encountered with other chemotherapy agents in brain tumor trials [8, 9].

The two articles in this issue evaluating treatment of recurrent malignant glioma illustrate several of the controversial issues facing the field of neuro-oncology. The first is the importance of establishing the specific pathologic diagnosis that may be modified by other prognostic factors, as demonstrated by the recursive partitioning analysis by Curran et al. [10]. The second major issue facing the interpretation of brain tumor clinical trials is the definition of response. The widely accepted response criteria, established by Macdonald et al. [11], evaluate the cross-sectional area of tumor on imaging studies have provided standardization of response. The patient must be on a stable or decreasing dose of corticosteroids to be suitable for response assessment. However, even with standardization of assessment criteria, response rates remain low for most glioma treatments and controversy remains regarding the significance of the 'stable disease' designation. Comparing the papers by Brandes et al. and Brada et al. illustrates this controversy. Brandes et al. use the established criteria and report a response rate of 22%, combining partial response with stable disease. In contrast, the manuscript by Brada reports only six month progression-free survival and does not use response as a measure of treatment efficacy. Brada et al. reflect the recent trend in neuro-oncology, comparing treatments by the absence of progression, setting aside issues related to defining response. This is understandable, given that the disease process is mired with complex images and determination of response is complicated by prior therapies such as radiation, radiosurgery and implantation of chemotherapy into the tumor bed. Criteria based on progression-free survival are slowly being established
for each glioma histologic subtype to determine whether a particular regimen has possible utility [12]. There are, of course, limitations to this analysis, such as the need to standardize frequency of evaluations; the need to clarify the definition of disease stability and assurance that only patients with progressive disease were enrolled in the trials.

The paper by Christodoulou et al. illustrates some of the issues facing studies of chemotherapy for brain metastases. Historically, few trials have explored the use of systemic chemotherapy for brain metastases. Those that were done showed only poor-to-modest response rates, with the exception of germ-cell tumors and lymphoma, whose treatment with initial chemotherapy has become widely accepted because of their very high response rates [13]. There has been concern regarding the delivery of most chemotherapy agents to brain lesions, although concern about the blood–brain barrier is unwarranted for brain metastases. The enhancement of these lesions by intravenous contrast agents indicates that the blood–brain barrier is breached. Trepidation nevertheless remains regarding the unique milieu of the brain and its possible impact on treatment success. More pertinent concerns of interpreting brain metastases treatment trials are related to the heterogeneity of the tumor types treated, and the timing of treatment in the course of the illness. In the study by Christodoulou and colleagues, brain metastases from a wide range of systemic cancers are treated. This reduces the ability to demonstrate responsive cancer histologies given the small number of each type of tumor treated. Previous studies focusing on a single cancer group, using a treatment regimen with established efficacy for the specific cancer, showed good activity [14, 15]. Additionally, many studies, including the current trial, evaluate the efficacy of chemotherapy late in the course of illness, used only after there has been treatment with first and often second-line therapies. In such a setting of recurrence, modest responses are anticipated when advancing systemic disease is treated with ‘salvage’ regimens. Limited response would logically be anticipated for brain metastases treated with second- and third-line regimens.

The three papers in this issue demonstrate that there is a high degree of enthusiasm for advancing the treatment of cancer in the nervous system. There is a need to carefully define the treatment population and measures of response, and to insure that the results of a trial can be adequately compared with results from other studies. The search for new and effective treatments for cancer of the nervous system continues. Well-tolerated, cytotoxic treatments, such as temozolomide, will likely be important components of future treatment regimens, combining conventional chemotherapy with the novel cytostatic treatments, such as angiogenesis inhibitors, differentiation agents and inhibitors of tumor infiltration and migration [16, 17]. Similar combination strategies may also be useful for brain metastases. The potential exists as well for chemotheraphy agents, such as temozolomide, to be used as radiosensitizers to reduce radiotherapy doses or as central nervous system prophylaxis for cancers with a high likelihood of developing brain metastases.

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References