Integrating bevacizumab and radiation treatment of brain metastasis: is there sense and sensibility in this approach?

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Abstract: The incidence of brain metastasis has increased over the past decade. Standard treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) and surgery for patients with operable lesions and either mass effect or need for histologic confirmation of the diagnosis. Patients are living longer due to improvements in systemic therapeutic approaches, included targeted therapies such as inhibition of vascular endothelial growth factor (VEGF) using the monoclonal antibody bevacizumab (Bev). A recent phase I trial (REBECA) investigated adding Bev to whole-brain radiation for patients with brain metastasis from solid tumors. In this Perspectives article, we discuss the results of the REBECA trial in context of advancements in radiation and medical oncology in the era of targeted therapies, and discuss pertinent questions of interest in this field.

Keywords: Brain metastasis; bevacizumab (Bev); whole-brain radiation; angiogenesis; vascular endothelial growth factor (VEGF)

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Introduction

The incidence of metastasis of systemic malignancies to the central nervous system (CNS) (brain metastasis) has increased significantly over the past decade. Incidence is most frequent in patients with lung cancer, breast cancer, or melanoma (1). Standard treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) and surgery for patients with operable lesions and either mass effect or need for histologic confirmation of the diagnosis. Patients are living longer due to improvements in systemic therapeutic approaches, including maturation of the field of molecular oncology and identification of rational targets for therapy. Incremental increases in overall survival have led to a new set of clinical challenges including attempts at effective therapeutic management of brain metastases and associated morbidities. Inclusion of patients with brain metastasis in clinical trials has paradoxically been extremely limited to date, but there is growing recognition of the need to change this paradigm in the modern era (2,3). Most of the concern has centered on perception of naturally worse prognosis and inherent risk of intracranial hemorrhage in this subpopulation (3). Recent studies and strategic approaches have combined knowledge of molecular pathways from systemic malignancies with high propensity for CNS metastasis (e.g., melanoma, lung) along with examination of efficacy of treatment of primary CNS tumors. Penetration of the blood-brain barrier (BBB) has presented a particular challenge in treating patients with both primary and secondary intracranial malignancies, thus some studies are also investigating methods for negating the barrier to improve drug penetration and efficacy.

Angiogenesis is an especially prominent molecular and cellular response to hypoxia and invasion in the heterogeneous tumor microenvironment for many solid tumor malignancies. There has been a great deal of investigation into this process at the cellular level, and investigation of treatment of systemic malignancies

with anti-angiogenic drugs, most prominently Bev, a monoclonal antibody that targets vascular endothelial growth factor (VEGF). To date, Bev has been FDA-approved for treatment of metastatic non-small cell lung cancers, recurrent glioblastomas (GBM), metastatic colorectal cancers, and others (4). It has also demonstrated degrees of efficacy in other forms of invasive malignancy, including atypical meningiomas (5), and found to improve progression-free survival but not overall survival in first-line treatment of glioblastoma (6,7) although there is some supportive evidence of stabilization of unresectable GBM in that setting (8,9). Success of the use of this agent in patients specifically with CNS metastasis has not been as well characterized. In 2014, Lévy *et al*. (10) reported results of REBECA, a phase I trial investigating the use of Bev in combination with whole-brain radiation therapy (WBRT) to treat patients with unresectable solid tumor brain metastases. This study represents one of several studies investigating the anti-angiogenic approach in this specific population, and is a first step toward designing rational clinical trials to address efficacy using this strategy in a patient with few valid therapeutic options.

REBECA: a phase I study of bevacizumab (Bev) for brain metastasis

REBECA was a single-arm phase I study with 3+3 dose-escalation design.

Twenty-one patients were enrolled during a 3-year span across six cancer centers in France. Thirteen of the 21 patients had breast cancer; the remaining patients had lung, ovarian, or unknown primary malignancies (10). Two of 19 (11%) experienced intra-lesional hemorrhage but no patient experienced parenchymal brain hemorrhage. Ten of 19 (53%) showed a response at 3 months which is the expected response rate with WBRT alone. Limitations of the study included relatively small number of enrolled patients, and lack of other representative cancers that commonly metastasize to the brain (e.g., melanoma and renal cell carcinoma, both of which have a relatively high likelihood of intracranial hemorrhage compared with other types of cancer). Further investigation in safety trials with these patient populations would be warranted to make accurate conclusions of Bev safety. Bev is used in treatment of metastatic renal cell carcinomas and in NSCLC. Thus the scenario is clinically relevant for patients on Bev who develop brain metastases and undergo WBRT, and/or SRS.

Radiologic assessment of brain metastasis response: new rules for assessing efficacy of treatment in the era of bevacizumab (Bev)

Until the past few years, assessment of objective responses of intracranial tumors to treatment was made by adhering to Response Evaluation Criteria in Solid Tumors (RECIST) (v 1.1). In 2010, the Radiologic Assessment in Neuro-Oncology (RANO) Working Group formulated a set of radiologic criteria for more accurately assessing response of primary malignant brain tumors (specifically gliomas) to therapy (11). In 2015, this Working Group established a similar set of consensus guidelines for radiologic assessment of brain metastases (12). The RANO criteria has been helpful for more accurate analysis of the effects of Bev on gliomas; likewise, incorporation of the new designated criteria will be helpful for future early and late-phase trials of Bev in brain metastases.

Strategically, there is also debate regarding the ability of monoclonal antibodies, including Bev and trastuzumab, to cross the BBB. How much penetration of drug is enough to achieve a meaningful clinical and measurable response? There is a widely held view that disruption of the BBB leading to CNS metastasis renders it more permeable not only to further micrometastases, but also to administered drugs. Part of the response process includes upregulation of VEGF, which in turn induces vascular permeability that permits tumoral growth of micrometastases. Methods that have been proposed to improve efficacy of BBB penetration of drugs include liposomal delivery and non-pharmacologic methods such as induction of hyperthermia (13). Furthering the debate on utility of Bev are studies questioning its efficacy in treatment of primary gliomas. Anti-angiogenic treatment relieves peri-tumoral edema, resulting in primary relief of tumor-induced symptoms in many patients. However, Bev may stabilize the permeabilized BBB, which would be counteractive by preventing adequate delivery of concurrently administered chemotherapeutic drugs (14). Thus there is concern about use of Bev on multiple fronts in gliomas that should also be addressed in future trials assessing Bev for intracranial metastatic tumors. In this era of molecular oncology, it will be imperative to also consider genomic differences in systemic malignancies and to acknowledge that these differing profiles and driving mutations may influence response between tumor types. Known differences in invasive capacity of metastatic CNS tumors compared with primary gliomas (less invasive

at the cellular level in the former) may also require a different strategic approach (15).

When to give bevacizumab (Bev): is concurrent administration the wrong approach?

Timing of administration of Bev in relation to radiation is also an aspect of interest scientifically. The REBECA study authors concluded from their study that Bev provided the best efficacy with RT when administered at a higher dose of 15 mg/kg three times (every 14 days) concurrent with WBRT (30 Gy/10 fractions over 2 weeks). Response rates in this study were modest even with this combination, which the authors propose as a starting point for evaluation in future phase II trials. Biologically, there is a potential paradox in terms of Bev efficacy: radiation-induced cellular stress may induce angiogenesis, which can create vascularity that may improve drug delivery to tumor tissue. Striking a balance of efficacious drug delivery with disruption of angiogenesis to prevent tumor growth is vital. One recent study using an *in vivo* preclinical model of breast cancer brain metastasis proposed preconditioning tumors with Bev in advance of (rather than concurrent with) chemotherapy (16). Conversely, "preconditioning" with RT first, followed chronologically by administration of Bev, may be more logical and beneficial by providing treatment at a peak of radiation-induced hypoxia. As the half-life of Bev is relatively long (21 days) (17), sequential administration (in either order) should be explored further in preclinical models as a different strategic approach to its use. The authors of the REBECA study proposed early administration of Bev (2 weeks before initiation of WBRT) to induce vascular normalization to enhance the effects of radiation (10). However, this strategy remains hypothetical and speculative at this point in time; data supporting this approach in preclinical models would be needed before pursuing this in human trials.

Bevacizumab (Bev) in combination with RT: lessons from treating primary brain tumors

Assessment of the safety of Bev in combination with RT is imperative, particularly due to past or residual fear of its risk of intracranial hemorrhage in patients with brain metastases. Bev in combination with salvage SRS has been examined in recurrent (refractory to prior irradiation as well as temozolomide chemotherapy) malignant gliomas and found to be well tolerated (18). Administration of adjuvant Bev following SRS resulted in a 3.1-month improvement in progression-free survival compared to SRS alone. The incidence of grade 3 and 4 toxicities was similar between the two groups (18). The principle that Bev would be effective in suppressing angiogenesis activated by radiation-induced expression of hypoxia-inducible factor 1 (HIF-1) may translate to treatment of brain metastases regardless of the radiation modality employed (19).

Is WBRT the correct radiation-based modality for concurrent bevacizumab (Bev)?

In the era of improved radiation modalities, we should also consider alternate radiation approaches including SRS, intensity-modulated radiation therapy (IMRT) or even proton beam therapy rather than WBRT for treating brain metastases when applicable. There is increasing concern about the utility of adding WBRT to SRS, especially in terms of effects of the former on worsening neurocognition (20,21). It is now well established that the converse, adding SRS to WBRT, improves survival in patients with single brain metastases, and in patients <65 years as well as those with well-controlled systemic disease, and higher graded prognostic assessment (GPA) scores (22,23). Studies demonstrating sufficient control of limited brain metastases with SRS alone (24,25) provide impetus for future evaluation of studies adding Bev to SRS rather than to WBRT. Considering the concerns expressed from the authors of RTOG 8205 detailing worsened neurocognition in patients receiving 1st-line Bev with radiotherapy of GBM, adding this to WBRT may compound this issue (7). The REBECA study authors point out that some patients are ineligible for SRS, and thus WBRT is their next best option. For example, 3 of the 21 patients in this study had four brain metastases (all in breast cancer patients), 1 of whom had heavy systemic burden of malignancy as well, and thus high chance of further intracranial recurrence (10). Likewise, in terms of prognostic assessment of enrolled patients using Recursive Partitioning Analysis (RPA) classification, only 5 of 21 patients had RTOG prognostic group Class 1 (Karnofsky Performance status ≥70, age <65, primary tumor controlled, absence of extracranial metastasis) (10). Thus the majority of patients truly had poor prognostic features that may have aligned with less benefit from SRS. Nonetheless, consideration could be given to trials incorporating Bev to SRS for patients with the good outcome features noted above per RPA or GPA assessments.

Conclusions

Ongoing questions include how to best balance treatment of primary systemic malignancy with treatment of intracranial metastasis of that malignancy. Differences may arise depending on context of vascularity of the primary malignancy, heterogeneity and discordance between primary tumor and metastatic lesions that metastasize to and thrive in the CNS microenvironment, and genomic profiles include identity of the driving mutation. Regardless of these factors, there is increased recognition that spatially, intracranial disease is compartmental and that prognosis, and possible response to Bev therapy, may in fact vary based on location within the brain parenchyma. Furthermore, all other parameters being equal, prognostic assessment may diverge based on whether a single metastatic lesion is solitary (i.e., absence of active detectable systemic disease) or present with systemic activity. In these cases, creative use of well-tolerated biologic agents such as Bev in combination with localized radiation modalities (focal irradiation and/or SRS) has potential as efficient approaches to improving prognostic outcome while sparing patients of potentially inefficient chemotherapies. The role of biological agents in the optimal management of brain metastases remains undefined. The REBECA study is among the first of hopefully many studies that will seek to address these issues.

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Footnote

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