Focal or combined modality for the management of brain metastasis: did high tech radiotherapy superseded drug-radiotherapy combination?

Major recent improvements of the efficacy of systemic therapies have challenged the fact that patients with metastases should only be managed in a palliative intent. This is particularly relevant for patients with brain metastases. In these patients, the suboptimal results of historical whole-brain radiation therapy (WBRT) have encouraged new strategies for optimizing control of intracranial metastases: combination with new drugs and technological developments based on new irradiation technologies [1].

Combination of molecular targeted agents (MTA) and irradiation has raised major expectancies [2]. However, there is still a major gap between the promise of preclinical investigations combining MTA and irradiation and the fact that since 2006, no concurrent MTA has shown its ability to improve outcome of patients receiving therapeutic irradiation [3]. In patients with brain metastases, numerous drugs have been tested in addition to WBRT in phase I–III trials. However, no combination has shown significant benefit over WBRT alone [4]. Actually, most studies included patients with various primary tumors and with various prognostic factors (recursive partitioning analysis status, number of metastases) [5].

There is a strong preclinical rationale for combining antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) with ionizing radiation. Unfortunately, clinical studies conducted in other indications have illustrated the discrepancy between the amount of positive preclinical results and the real benefit in patients. In sharp contradiction with the strong preclinical background, combination of anti-VEGF therapies and irradiation has shown either little impact in terms of efficacy in rectal cancer [6] or major concerns regarding tolerance in lung nonsmall-cell lung cancer [7, 8]. Recently, two phase III studies have shown that addition of bevacizumab to standard chemoradiation for glioblastoma failed to improve survival, at the expense of a higher rate of serious adverse events associated with bevacizumab [9, 10].

The Rebeca trial examined the safety of combining bevacizumab with WBRT for the treatment of brain metastases [11]. Since WBRT was used, Levy and colleagues appropriately opted for a phase I trial design. These data are important from the safety point of view. Although toxicity could be feared, given the large irradiated volume, no major toxicity inside the radiation field was observed. In the clinic, it is an important point to solve the issue of the discontinuation of bevacizumab when palliative irradiation is required. We now have arguments to answer that bevacizumab and WBRT can be carried out simultaneously or at least that it is not necessary to wait for 12 weeks (4 half-lives) after the last perfusion of bevacizumab before delivering WBRT. However, it would be important to thoroughly examine the neurocognitive effects of the combination, since these patients are now likely to survive long enough to develop late WBRT neurotoxic effects.

If we consider tumor response data, two questions come-up, first do we have a signal in the current series and second are the results any better than the baseline comparator? The clear regression of tumor volumes is encouraging but has to be interpreted cautiously. Some authors suggested that responses seen in bevacizumab-treated patients could be partially due to palliation of necrosis and edema rather than a response of targets, questioning the relevance of RECIST criteria [12]. Although survival times compare favorably to what was reported in previous trials combining WBRT with other radiosensitizers [4], the medical needs should be reconsidered before embarking on randomized phase II/III trials that would examine survival as the primary target. Information regarding histological subtypes would be also useful, since there is a growing place for systemic therapies only when molecular targets are identified in selected patients, in particularly in breast or lung cancer patients who accounted for more than 70% of patients enrolled in the Rebeca trial [1]. The noncomparative phase II study BRAIN has examined the combination of bevacizumab plus first-line chemotherapy (carboplatin/paclitaxel) or second-line erlotinib in the treatment of previously untreated asymptomatic brain metastases from nonsquamous nonsmall-cell lung carcinoma. In first-line therapy, median progression-free survival (PFS) and overall survival (OS) times were 6.7 and 16 months, respectively, which is not very far from the results of the Rebeca trial without WBRT (7.1 and 13.3 months, respectively) [13].

An important point to be discussed when providing further development of the tested combination is that the selection of patients in this study overlaps with stereotactic radiotherapy indications. There is level I of evidence that addition of WBRT to radiosurgery for patients with one to three brain metastases decreases intracranial relapses but at the expense of neurocognitive effects and without survival improvement [14–16]. Consequently, it is preferable to postpone WBRT in patients with a long expected survival. The widespread diffusion of frameless, noninvasive stereotactic techniques has reinforced this strategy in selected patients with oligometastases [17]. The tolerance of this treatment is extremely good and the >90% response rates are sustained in the majority of cases. Stereotactic radiotherapy is considered as a mainstay for patients with one to three metastases to the brain and offers the advantages to limit the irradiation of normal brain, an important aspect for functional issues. Moreover, it provides ‘ablative’ radiation doses leading to a
massive destruction of irradiated tumor cells, a situation where ‘sensitizers’ are no longer needed except if biomarkers define groups at risk for recurrence or sensitivity to bevacizumab [18]. Anyway, the extremely focused irradiation provided by stereotactic devices does not preclude examining the potential toxicity of high doses per fraction delivered with antiangiogenic agents. A recent phase II trial in glioblastoma has shown safety and effectiveness of combining bevacizumab, temozolomide, and hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma [19].

To conclude, the Rebeca trial provides meaningful information for clinicians on the feasibility of combining bevacizumab and WBRT in patients with brain metastases. Although the optimal strategy for treatment of brain metastases remains to be refined, when considering the two main development axes of radiotherapy, high-tech radiotherapy seriously challenges pharmacomodulation at this stage.

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