Sense and sensibility to early combine bevacizumab to radiation treatment of brain metastasis: reply to Lou and Sperduto

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We thank Lou and Sperduto (1) for their comments regarding the results of our REBECA trial [a phase I study designed to assess the safety of bevacizumab (BEV) in combination with whole brain radiation therapy (WBRT) for brain metastases (BM) of solid tumors (2)]. They highlighted the interest of exploring VEGF-based therapy in the context of radiation therapy of BM, as well as the issues of such an approach.

They pointed out the absence of patients with melanoma or renal cell carcinoma in our population (mostly represented by breast cancer patients). That may be explained by the fact that these tumors may now benefit from specific targeted therapies (particularly BRAF and checkpoint inhibitors) and by the lack of safety information of an approach combining these specific targeted therapies with BEV. However, considering the growing use of targeted treatments across multiple tumor types, we agree with the assumption that combinations with angiogenesis inhibitors must be explored in the future, especially in lung cancer.

The timing of the delivery of anti-angiogenic agents when combined with radiation therapy was also questioned. Preclinical data support that the synergic effect of these approaches is based on (I) the normalization of tumor vascularization, which improves oxygenation and counteracts the negative effect of hypoxia on radiation effect; and (II) the inhibition of VEGF protective effect on endothelial cells. This biological rationale explains our design with an early administration of BEV before the onset of WBRT, followed by two other injections during the course of treatment (in the intent to "provide the treatment at a peak of radiation-induced hypoxia" as proposed by Lou and Sperduto). Moreover, the results from two large randomized studies combining radiotherapy with BEV for patients with malignant gliomas (3,4) seem indicate a better outcome (both for efficacy and cognitive safety) when anti-angiogenic treatment was delivered from the start of radiotherapy (3) rather than during the fourth week of radiotherapy (4). This supports the beneficial effect of an early introduction of BEV.

Finally, we agree with the comment about the growing place of stereotactic radiotherapy (SRT) for BM. The REBECA trial was designed for BM patients eligible to WBRT only (assuming that at least 50% of lung cancer and some breast cancer patients are not eligible to SRS because of too many BM). However, many BM patients are eligible to SRS and it could be assumed that the good safety profile of BEV administration with a large radiation volume may also be expected in the context of its combination with smaller volume as in SRS. This assumption seems confirmed by some recent data of SRS combined with BEV in patients with recurrent malignant gliomas, confirming the feasibility of this approach with a good safety profile (5-8). Clinical evaluation of BEV combined with SRS through a prospective trial is urgently needed for patients with BM.

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Footnote

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References

1. Lou E, Sperduto PW. Integrating bevacizumab and radiation treatment of brain metastasis: is there sense and sensibility in this approach? Ann Transl Med 2016;4:36.
2. Lévy C, Allouache D, Lacroix J, et al. REBECA: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours. Ann Oncol 2014;25:2351-6.
3. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-22.
4. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
5. Cuneo KC, Vredenburgh JJ, Sampson JH, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 2012;82:2018-24.
6. Cabrera AR, Cuneo KC, Desjardins A, et al. Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: a prospective trial. Int J Radiat Oncol Biol Phys 2013;86:873-9.
7. Clark GM, McDonald AM, Nabors LB, et al. Hypofractionated stereotactic radiosurgery with concurrent bevacizumab for recurrent malignant gliomas: the University of Alabama at Birmingham experience. Neurooncol Pract 2014;1:172-177.
8. Hasan S, Chen E, Lanciano R, et al. Salvage Fractionated Stereotactic Radiotherapy with or without Chemotherapy and Immunotherapy for Recurrent Glioblastoma Multiforme: A Single Institution Experience. Front Oncol 2015;5:106.

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