Second-Line Chemotherapy in Recurrent Glioblastoma – Still Controversial

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In this issue of Oncology Research and Treatment, Carvalho and Colleagues investigated in a retrospective study the role of second-line treatments in patients with recurrent glioblastoma [1]. As yet, the use of second-line agents remains the most debated topic in this field, and after more than 10 years of studies a clear role for the use of bevacizumab has not been completely established yet. In fact, the first data published in 2005 on response rate and progression-free survival with bevacizumab raised some interest of the scientific community [2]. As a consequence, a first generation of single arm phase II trials were conducted in patients with recurrent glioblastoma [3–5], confirming that bevacizumab was able to provide high rates of radiological responses (30–60%) and progression-free survival at 6 months (30–50%). In particular, the BRAIN and the NCI 06-C-0064E trials [4, 5] led to accelerated FDA approval of use of bevacizumab in these patients. However, EMA did not approve the treatment due to the lack of direct comparison of bevacizumab with standard chemotherapy in these studies, and also due to the limited reliability of neuroradiological findings using antiangiogenic agents.

A second generation of randomized phase II trials was launched including a nitrosourea-based calibration arm ( fotemustine in the AVAREG trial [6], and lomustine in the BELOB trial [7]). In the BELOB trial the combination of bevacizumab and lomustine was also investigated. Despite the fact that these trials were not comparative, the results suggested that bevacizumab was able to obtain similar results in terms of survival rates with respect to chemotherapy, but with a different toxicity profile. Moreover, results were surprisingly superimposable across the AVAREG and BELOB studies, providing an important benchmark for future trials. Data about the combination of bevacizumab and lomustine were also considered worthy of further investigation in a phase III study, and the EORTC re-designed a randomized study with the aim to compare lomustine alone versus a combination of lomustine and bevacizumab. The results of the study of Carvalho et al. [1] are in line with what was obtained in the previous bevacizumab studies, and they suggest that this antiangiogenic agent could be a potential alternative to chemotherapy in recurrent disease.

Despite the increasing scientific knowledge about the use of bevacizumab in glioblastoma treatment some aspects about this agent still remain controversial. For instance, the updated Response Assessment in Neuro-Oncology (RANO) criteria [8] have not yet been prospectively validated, and disease assessment with bevacizumab remains challenging: neuroradiological predictors of outcomes are needed, as well as characterization of molecular profiles that could help clinicians in selection of possible responders amongst patients.

While waiting for studies that could clarify these aspects, clinical factors may help physicians choosing the best treatment: patients’ age [6], comorbidities, and previous toxicities to temozolomide may help in the decision for the best therapy.

Disclosure Statement

The Author declares no conflict of interest.
References


