Actas de Investigación Oncológica

Reflexión

¿Is there nowadays place for antiangiogenic therapy in relapsed glioblastoma?

Kevin Doello[1], Victor Amezcua[2], Raquel Luque[1]

1. Servicio de Oncología Médica. Hospital Virgen de las Nieves, Granada
2. AstraZeneca, Cambridge, UK

Autor de correspondencia: Kevin Doello
Correo electrónico: kevindoello@gmail.com

Dear editor. As it is well known, antiangiogenic therapy based on bevacizumab for relapsed glioblastoma is a controverted topic. Its rate of response is over 20-25% with a variable mOS. BRAIN study, completed in 2007, compared bevacizumab to bevacizumab plus irinotecan. Overall response rates (ORR) were 28.2% and 37.8% with a 6 months PFS of 42.6% and 50.3%, respectively. Later, a single-arm study evaluated 48 recurrent glioblastoma patients treated with bevacizumab and found an ORR of 35% and a 6 months PFS of 29%. Several studies have also evaluated the use of bevacizumab in combination regimens. The BELOB trial was a randomized phase 2 study of 148 patients with recurrent glioblastoma randomized to lomustine, bevacizumab, or both. Combination therapy resulted in a 6 months PFS of 41% compared to 11% and 18% with a mOS at 9 months of 59% compared to 43% and 38%. Based on these results, a phase 3 study (EORTC 26101) was developed to compare lomustine versus lomustine plus bevacizumab. There was no significant difference in mOS, although median PFS was increased from 1.5 to 4.2 months for combination therapy. Despite the approval of bevacizumab, several phase 3 clinical trials have failed to show survival benefits. However, the experience is that there is responders with clinical benefits and tumoral responses in spite of clinical trial results. Therefore, the main problem is the absence of predicter markers of response.

According to our retrospective experience, we obtained 22 patients and classified them according to pathological groups: primary (classical, proneural and mesenchymal) and secondary. Mesenchymal were defined as p53 negatives, S100 and/or vimentin positives. Glioblastoma with rabdoid or sarcomatoid properties were also included as mesenchymal ones. The rate of response to bevacizumab was 27% in our patients. There were 6 patients with mesenchymal phenotype (5 responders, 1 non responder). 9 with classical (9 non responders), 4 with proneural (4 non responders) and 4 secondary glioblastomas (1 responder, 3 non responders). The Chi-Square value for the relationship between mesenchymal phenotype and response to bevacizumab is 14,437 and P value is 0,002. Moreover, one of these responders with a mesenchymal phenotype have a disease free interval of 7 years and is still alive nowadays.

Our experience in patients reveals that it would be especially important the selection of patients for bevacizumab therapy. Unlike other targeted therapies, no established biomarkers currently exist to predict

response to bevacizumab. Tissue, blood, and imaging markers are all under investigation. Data suggest that the treatment of patients with glioblastoma with low doses of bevacizumab (5 mg/kg per week or 7.5 mg/kg every 3−4 weeks) may be superior to standard dosing. Targeting several pathways or combining anti-angiogenic agents with other drugs may overcome the development of resistances and increase the rate of response and survival.