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Circulating endothelial cells and progenitors in recurrent high-grade gliomas treated with bevacizumab and irinotecan.

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Abstract

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Background: Bevacizumab (Bev), a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), has shown significant activity in a subset of patients with high grade gliomas (HGG): to date no biological marker can predict the treatment benefit. Circulating endothelial cells (CEC) and progenitors (CEP) have been observed in cancer patients, reflecting ongoing tumor angiogenesis.

Methods: Forty-seven HGG patients (38 glioblastoma, GB; 9 anaplastic astrocytomas), relapsing after radiotherapy and temozolomide, were treated every 2 weeks with Bev (10 mg/kg) and irinotecan (125 or 340 mg/m² depending on EIAEDs use). Adverse events were graded based on the CTC-AE v3.0. Before first treatment and every 8 weeks MRI and CEC and CEP assessment were performed. Radiological responses were assessed based on RANO criteria. CEC and CEP were enumerated in healthy controls (n=37) and patients by six color flow cytometry as Syto+CD45-CD31+P1h12+ and Syto+CD45-CD31+/CD133+ cells, respectively. The Kaplan Meier method estimated survival functions.

Results: Median age was 53 years (15-66), median Karnofsky Performance Status 70 (50-100). Median number of prior chemotherapy treatments: 2 (1-4). Median follow up: 6.5 months. Median PFS and OS were 6 and 10 months, respectively. For GB, 6M-PFS was 47% and 6M-OS 68%. No central nervous system hemorrhages were detected. No patients developed grade 3-4 hematological toxicity. One patient experienced a small intralesional bleeding. When compared to controls, HGG patients had a significantly lower CEC and CEP at baseline (88.5±50 vs 140±171, p=0.03; 73.9±62.3 vs 181±167 p=0.001), but higher CD109+ CEC levels (91.5±78.3 vs 31±29). Interestingly, patients with higher baseline level of CEC, CEP and CD109+ CEC showed clinical benefit (i.e. PFS≥4 months): 118.8±57.4 vs 80.8±43.2, p=0.002; 99.7±74d vs 60.4±51.7, p=0.04; 126.8±97.1 vs 76.3±64, p=0.002. No correlation between baseline tumor volume, 6M-PFS and CEC or CEP enumeration was found.

Conclusions: Investigation on CEC and CEP could contribute to a better understanding of the action of Bev in HGG patients and help to identify responders.