First-line bevacizumab for glioblastoma: what do recent Trail results mean for future treatment?

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For those who did not attend this year's American Society of Clinical Oncology plenary session or read about it later on, a new enigma emerged with Gilbert's talk, who presented this study so calmly and left the audience perplexed by reporting that patients with glioblastoma who had been treated with bevacizumab in addition to the current standard of care showed worse results on some neurocognitive tests compared with patients treated with standard therapy only [1].

The worse outcomes were mainly observed in the Trail making tests A and B. These tests involve several areas of the cortex, as the patients are asked to connect as rapidly as possible the numbers from one to 20 (Trail making test A) or numbers and letters (1-A, 2-B, 3-C and so on) with a pencil. My own performance in these tests is not so good, as I have an amblyopic eye and need a strong varifocal glass for the 'working other'. This personal experience taught me that the performance in neurocognitive testing may depend not only on cognition, but also on visual acuity, which can also be compromised by the treatment of glioma through conditions such as persistent brain edema after radiation

therapy, dexamethasone comedication, and by bleedings that could be caused by bevacizumab or thrombocytopenia. Gilbert's talk also described that health-related quality of life was compromised in a significant number of patients treated with bevacizumab upfront when compared with patients treated with the actual standard of care (maximal feasible resection, conformal radiotherapy up to 60 Gy with 2 Gy per fraction and concomitant and adjuvant chemotherapy with temozolomide).

This lends itself to the question, is bevacizumab inadequate for the treatment of patients with newly diagnosed glioblastoma?

There are two randomized Phase III trials encompassing over 1500 patients, Radiation Therapy Oncology Group (RTOG) 0825 and AVAglio, which, so far, show no survival advantage when adding bevacizumab as first line, and now there is the intriguing data on the compromised neurocognitive function and quality of life from the RTOG 0825 trial.

My previous personal experience with bevacizumab was limited to patients at time of relapse. As the EMA did not approve bevacizumab for malignant gliomas in

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Europe, the drug is not reimbursed and I guess that, not only in my institution, it remains challenging to obtain bevacizumab for patients with gliomas. Such measures effectively limit the number of patients treated, favoring those with better compliance in the past, those who will keep blood pressure diaries, be able to come to the hospital biweekly for their infusions and inform their physicians in case of any planned surgical procedures. In those selected patients treated with bevacizumab for relapsed glioblastoma, we had sometimes observed dramatic improvements of their neurological symptoms with recovery from paresis or blindness lasting for several months, as long as the tumor did not progress. Therefore, the result of worsening in quality of life in the cohort of patients treated with upfront bevacizumab described at the American Society of Clinical Oncology plenary session was initially perceived as contradictory to my positive personal experience with the drug.

Moreover, a population-based analysis by Johnson *et al.* has shown an improvement in patient survival in the USA of 2 months after the approval of bevacizumab for recurrent disease, comparing survival data from Surveillance, Epidemiology and End Results from 2008 to 2010 [2]. This is a very strong indicator in favor of bevacizumab as it has shown a similar improvement in survival duration as when temozolomide was introduced.

Meanwhile, the data from neurocognitive tests of both RTOG 0825 and AVAglio trials will be analyzed thoroughly by neuropsychologists and the potential impact will be discussed again within the community, however, the optimal treatment for glioblastoma remains to be defined.

We need to think about which questions were solved by these two trials, and how we should proceed to improve the outcome of our patients.

We should be very grateful to the colleagues participating in RTOG 0825 who noticed those subtle changes leading to this reflection of the already accumulated data.

Animal experiments on rats with irradiation to the CNS show the breakdown of the blood–brain barrier and that VEGF is upregulated physiologically after radiation by astroglial cells [3]. At a dosage of 10 mg/kg every 2 weeks, bevacizumab is able to block VEGF for months, and probably also blocks the physiologically secreted VEGF, which is required for the reparation of tissue damage caused by the radiochemotherapy. Our current knowledge does not elucidate how in this individual case, we could obtain inhibition of tumor vessel growth without endangering physiological recovery mechanisms after chemoradiation. Dosage and timing of bevacizumab will have to change in order to avoid neurocognitive damage and to hopefully improve outcomes. More work is required, perhaps some smaller and more sophisticated studies that should include neurocognitive monitoring and of course quality-of-life recording.

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