Bevacizumab therapy for glioblastoma: a passionate discussion

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Few, if any, topics have ignited the passions of the global neuro-oncology world more than the role of bevacizumab in the treatment of patients with glioblastoma multiforme (GB). From its relatively recent anecdotal [1] and single institution trials of recurrent disease [2,3] to the multi-institutional study that led to US FDA approval of bevacizumab in the USA for recurrent GBM [4], to single-arm trials of newly diagnosed patients [5,6] and finally to two randomized Phase III trials in newly diagnosed patients presented at the 2013 meeting of the American Society of Clinical Oncology [7,8], strong passions have been ubiquitous and at this point predictable and anticipated.

Why then has a pharmaceutical agent so inflamed the world's neuro-oncologists and related specialists? The answers lie, as in all controversies, with the disparate interpretation of the available data held by the leaders and their followers in this field.

Certain basic facts are immutable and do not appear to be controversial. Bevacizumab given with irinotecan was initially shown by Stark-Vance to produce extraordinary radiographic and clinical improvements in patients with GBM refractory to

many prior treatments [1]. Vredenburgh *et al.* subsequently demonstrated prodigious radiographic and clinical responses in single-arm clinical trials [2,3], although it became clear that T1-contrasted MRI could prove misleading, requiring the consideration of fluid-attenuated inversion recovery imaging, a concept subsequently formalized into the modified Revised Assessment in Neuro-Oncology (RANO) criteria [9].

The BRAIN Trial [4], incorporating this important observation, confirmed the response rate of bevacizumab alone or in combination with irinotecan, leading to FDA approval of bevacizumab in patients with recurrent GBM. This became a major point of contention in Europe, and in some, but fewer, US institutions, because a true comparative control group was not included. Nevertheless, it is safe to say that although there will always be skeptics who doubt the benefits of any new agent, bevacizumab does help patients with recurrent disease. However, it certainly does not help all such patients, but currently we do not have any test or genetic profile to reliably differentiate responders from

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nonresponders. Critics will say that bevacizumab makes it harder to treat patients whose disease progress while receiving it, yet are hard pressed to identify a treatment that is more meaningful. Concerns regarding the patterns of failure, specifically proangiogenic enhancing disease at the initial presentation site [4,10] versus increased proinvasive diffuse disease [11], are frequently voiced with different reports indicating a change versus no change compared with nonbevacizumab-treated patients who demonstrate recurrent tumor. Questions thus have been raised as to whether bevacizumab should be given at first recurrence or at a later recurrence. Proponents of this appear unfazed by the observation that many patients do not receive any therapy as subsequent recurrences are seen.

The issues regarding the treatment of patients with newly diagnosed GBM are even more contentious. The definitive studies are AVAglio and RTOG 0825, which reported at the American Society of Clinical Oncology 2013 meeting results so different and confusing that it led the executive director, Max Wallace, of one of the leading brain tumor advocacy groups in the world, Accelerate Brain Cancer Cure, to ask for a FDA review of both trials [12]. In essence, both groups reported similar overall survival with no differences in bevacizumab- or placebo-treated patients, an observation probably, although not definitively, owing to the crossover of patients on the placebo arm who subsequently received bevacizumab, as well as owing to the vast majority of patients who initially got bevacizumab but discontinued it at recurrence [13]. The progression-free survival in both studies showed similar increases with similar p-values, but owing to statistical design differences, only the AVAglio study considered the increase meaningful. Most disturbing and extremely controversial were the disparate

results showing the neurocognitive/quality of life benefits (AVAglio) versus detrimental effects (RTOG 0825) produced by bevacizumab. Howard Fine (New York University Langone), in what we consider to be a truly brilliant summation, addressed these concerns and argued for a third party review of all the data in both trials.

So where are we now? We know that bevacizumab works in the treatment of recurrent GBM; that not all patients derive benefit; it increases progression-free survival in patients with newly diagnosed tumors; it may or may not enhance or worsen neurocognition/quality of life in these patients; and, in our opinion, it will enhance survival in specific cohorts of patients with newly diagnosed and recurrent GBM. Furthermore, although there are those who suggest bevacizumab should be simply used as a salvage therapy, we should note that even on a clinical trial with a mandatory crossover (RTOG 0825) less than half the patients ever received bevacizumab at tumor progression. One can assume this will be even lower in patients who were not treated in a clinical trial. It is very easy to criticize work in any field, but we suggest that time is better spent trying to make improvements rather than seek reasons why something others did is of no merit. We eagerly await the FDA reviews of the AVAglio and RTOG 0825 trials.

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