Bevacizumab for Newly Diagnosed Glioblastoma

TO THE EDITOR: Patients who receive some drugs for cancer live no longer than controls, although clinical benefits can be modest and differ between similar studies. Two trials of bevacizumab for glioblastoma, the Radiation Therapy Oncology Group (RTOG) 0825 trial reported by Gilbert et al. (Feb. 20 issue) and the Avastin in Glioblastoma (AVAglio) trial reported by Chinot and colleagues in the same issue, exemplify these points, and their findings are a clinical watershed. Although both trials showed no increase in overall survival and similar adverse effects of bevacizumab, AVAglio, the trial sponsored by a pharmaceutical company, showed maintenance of quality-of-life outcomes, whereas RTOG 0825, the trial sponsored by the National Cancer Institute, showed decreased quality of life. Chinot et al. claimed that their updated imaging criteria “explained,” in part, the polar-opposite conclusions about quality of life reached by Gilbert et al., but they provided no quantitative data to support their assertion. We are thus faced with a situation in which an expensive drug with known harms is used on the basis of subjective quality-of-life criteria and in which substantive clinical benefits are unclear. To move from this imbroglio to solid science-based medicine requires release of de-identified data and the independent evaluation of these data. Anything less exposes patients to known harms for unknown gains and physicians to the dilemma of whether to prescribe a drug of questionable efficacy.

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Dr. Gilbert and Colleagues Reply:
The letter from Haines and Gabor Miklos underscores the importance of comprehensive analyses of outcomes measures to assess clinical benefit in pivotal clinical trials. In the RTOG 0825 trial, we incorporated the same measure of health-related quality of life — the European Organization for Research and Treatment of Cancer quality-of-life questionnaire with a brain-cancer module (EORTC QLQ-C30/BN20) — that was used in the
AVAglio trial, as well as an additional measure of symptom burden and three tests of neurocognitive function. These measures were shown to provide important outcomes information in an earlier phase 3 clinical trial involving patients with brain tumors. Unlike the AVAglio trial, in which the primary quality-of-life analyses were based on time to either deterioration in quality-of-life measures or tumor progression, our analyses evaluated longitudinal changes in the EORTC QLQ-C30/BN20 in patients without disease progression. Similar findings across all assessment measures in our trial provided confirmation that the results reflected the experience of the patients and that the differences between the two study groups were real. Further analyses comparing the quality-of-life outcomes of the RTOG 0825 and AVAglio trials could be of value but may be limited by specific differences in data collection between the two studies.

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DR. CHINOT AND COLLEAGUES REPLY: Although no other drugs evaluated since 2005 for use in patients with glioblastoma have shown activity, bevacizumab, as compared with placebo, was associated with a 4.4-month increase in median progression-free survival (from 6.2 to 10.6 months, an increase of 71%) in the AVAglio trial. These findings, which were confirmed by an independent review, were similar to those observed in RTOG 0825. These results should not be regarded as subjective, but rather as a positive outcome reinforced by clinical measures with value for patients. We did not claim that bevacizumab, as compared with placebo, improved quality of life, but rather that good quality of life was maintained for a longer time. The reasons for the discrepancy between our quality-of-life findings and the negative effect of bevacizumab on some quality-of-life domains reported at specific time points in RTOG 0825 remain a major challenge. To address these important discrepancies, we and the sponsor fully support an independent review of both quality-of-life and magnetic resonance imaging data. Indeed, these data may be linked, given the difference in tumor assessment criteria used in the two studies.

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Pregabalin versus Pramipexole for Restless Legs Syndrome

TO THE EDITOR: Allen et al. (Feb. 13 issue) provide very useful clinical information about pregabalin for restless legs syndrome (RLS). The careful differentiation of augmentation from loss of efficacy is especially remarkable. In this context, one may wonder how frequent the latter occurred in this trial, because pregabalin has been associated with the potential for abuse in some specific populations and might therefore lead to loss of efficacy. With regard to the outcome of the trial, we would like to ask the authors how they dealt with the potential confounders of depressive and anxiety disorders, which are frequent coexisting conditions in patients with RLS.

One could assume that pregabalin at least partially reduced symptoms of anxiety, whereas pramipexole might have had a positive effect on depression. If these potential effects are not

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