Bevacizumab Plus Irinotecan in Recurrent Glioblastoma

To the Editor: I congratulate Vredenburgh and colleagues for their article further supporting the role of bevacizumab and irinotecan in patients with recurrent glioblastoma (GBM). This article, an earlier article from the same group, a small series from the University of California, Los Angeles group, and the first report by Stark-Vance of this drug combination all seem to support the thesis that antiangiogenic therapy has substantial activity in recurrent GBM.\(^1\)\(^-\)\(^4\) Several issues regarding the article are relevant and warrant discussion.

The article builds on prior experience with this regimen (administration once every 2 weeks) and suggests no advantage to an alternative drug schedule (irinotecan administered weekly for 4 weeks every 6 weeks, and bevacizumab once every 3 weeks). Not clear, however, is whether a simpler regimen of irinotecan and bevacizumab administered every 3 weeks (a regimen of irinotecan used in the majority of glioma trials) may be equally as efficacious and more convenient.

Perhaps most challenging to fathom is the apparent activity of the regimen when one considers the extremely limited single-agent activity of irinotecan in recurrent GBM reported from multiple sources.\(^6\)\(^-\)\(^10\) The use of irinotecan in this empiric regimen by Stark-Vance\(^3\) was based on a single report (never substantiated) regarding anti-GBM activity, and the emerging activity and novel mechanism of action of bevacizumab in a variety of systemic cancers. Vredenburgh et al suggest potential mechanisms of action for bevacizumab (targeting the microvascular niche of glioma stem cells, forced normalization of the GBM vasculature) but less clear is why use irinotecan? Notwithstanding irinotecan penetration into brain parenchyma and a non–cross-resistant mechanism of action, why not consider alternative cytotoxic chemotherapies with improved single-agent activity (ie, nitrosoureas, phosphoramides, or platinoids) in combination with bevacizumab? Nonetheless, the brain tumor community has quickly adopted this regimen and patients increasingly demand this treatment as a new standard of care for patients with recurrent high-grade gliomas if not otherwise eligible for an investigational trial. Remarkably, the published data set on which this treatment shift has occurred is fewer than 80 patients.\(^1\)\(^-\)\(^5\)

Another challenging aspect to this regimen is pharmacoeconomic. Both irinotecan and bevacizumab are extremely expensive chemotherapeutics (pharmacy costs at the University of Washington [Seattle, WA] for irinotecan are approximately $4,000 [for 125 mg/\(m^2\)] to $9,000 [for 340 mg/\(m^2\)] per dose; bevacizumab is approximately $9,000 per dose), and at least for bevacizumab, are not covered by many insurers (eg, Medicare). On the basis of the response data of Vredenburgh (42% 6-month progression-free survival), an average treatment of 6 months would cost between $169,000 and $234,000 for pharmacy-incurred charges only. How to subsidize these costs outside of a sponsored clinical trial is unclear; an equally distressing fact is that this therapy is available only to patients with third-party payers willing to incur this charge. What of the medically disenfranchised patients with either no coverage or limited coverage? At present, these patients are excluded because of economic factors from the apparent benefits of this regimen.

A last consideration of this regimen and perhaps a class effect of antiangiogenic agents is the issue of craniotomy site dehiscence, an adverse effect unique to brain tumors and not previously commented on by Vredenburgh et al. Within this calendar year, our neuro-oncology group has seen four instances of craniotomy site dehiscence after re-operation for recurrent GBM and subsequent treatment with irinotecan and bevacizumab. In all instances chemotherapy was instituted 4 to 6 weeks after re-operation and with visual inspection confirming wound closure. Dehiscence occurred 2 to 6 months after the onset of treatment with irinotecan and bevacizumab. Although dehiscence occasionally can be seen after multiple same-site craniotomies through a compromised previously irradiated scalp, our experience suggests this is uncommon. In addition, we have seen a similar phenomenon in a single patient treated with sorafenib as salvage therapy for recurrent GBM, suggesting this may be a newly observed antiangiogenic class adverse effect specific to brain tumors. In all patients in whom dehiscence occurred, re-operation was required, which in addition mandated discontinuing what had previously been an effective salvage therapy. Rapid recurrence of the GBM was also observed in all of these patients and all but one quickly died as a result of disease progression. As noted by others, the initial concern regarding the potential for increased intratumoral hemorrhage with bevacizumab therapy has not been observed; however, craniotomy site dehiscence may be an emerging and perhaps underappreciated unique adverse effect in this patient population.

These comments are not meant to diminish the results of this elegant study, notable for determination of the activity of this regimen in a well-designed trial; rather, the comments reflect the difficulty encountered in treating patients with this disease and the lack of standardization regarding treatment of recurrent GBM.

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Author’s Disclosures of Potential Conflicts of Interest
The author(s) indicated no potential conflicts of interest.

References

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In Reply: We would like to reply to the letter from Marc Chamberlain regarding our article entitled “Bevacizumab Plus Irinotecan in Recurrent Glioblastoma.” Chamberlain raises a number of important issues and makes many good points.

The first issue was the schedule of irinotecan. We chose a regimen of administration once every 2 weeks with both irinotecan and bevacizumab to limit the toxicity. The regimen of administration every 3 weeks may be simpler, but the dose of irinotecan will be increased and we did not want to stop the trial because of toxicity. With our experience, the schedule of administration once every 3 weeks for irinotecan and bevacizumab may be as efficacious and tolerable.

The second issue raised by Chamberlain is the use of irinotecan in this regimen. We combined irinotecan with bevacizumab for three reasons. The first reason is that chemotherapy and bevacizumab is more active than bevacizumab alone in most malignancies. The second reason was that irinotecan has a different mechanism of action than temozolomide, so we were trying to limit cross-resistance. The third reason for combining irinotecan with bevacizumab is the experience in colorectal carcinoma and the US Food and Drug Administration approval of irinotecan and bevacizumab. I agree with Chamberlain that alternative cytotoxic chemotherapies may be equally active, and we eagerly await the results of ongoing clinical trials. All of these patients had received temozolomide and radiation therapy, and we hypothesize that irinotecan and bevacizumab may be as efficacious as O6-methylguanine-DNA methyltransferase-unfavorable tumor.

The third issue that Chamberlain raises was the pharmacoeconomics of anticancer therapy. We agree that the pharmacoeconomics of cancer care is a contentious issue and needs to be addressed. We feel fortunate that we finally have an active regimen against recurrent glioblastoma that allows us to worry about pharmacoeconomics.

The final issue raised by Chamberlain was craniotomy site wound dehiscence. We agree that this is a potential problem, and the concurrent administration of antiangiogenic agents and dexamethasone may increase the risk of wound dehiscence. We have had some patients with craniotomy site dehiscence as well as dehiscence of their port-a-cath sites. The issue of wound dehiscence requires extensive patient and provider education, and is one of the potential limitations of this promising therapy.

We appreciate Chamberlain’s comments, and hope that the combination of irinotecan and bevacizumab is the beginning of a new wave of therapies for malignant gliomas.

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