Title

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Journal

Journal of Clinical Neuroscience, 22(1)

ISSN

0967-5868

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Publication Date

2015

DOI

10.1016/j.jocn.2014.05.054

Peer reviewed

Journal of Clinical Neuroscience 22 (2015) 35–39

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Timing of surgery and bevacizumab therapy in neurosurgical patients with recurrent high grade glioma

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ARTICLE INFO

Article history:
Received 30 September 2013
Accepted 24 May 2014

Keywords:
Bevacizumab
Recurrent glioblastoma multiforme
Surgery

ABSTRACT

Malignant gliomas continue to have a dismal prognosis despite all available treatments and advances made in understanding molecular mechanisms and signaling pathways. Conventional treatments, such as surgery, chemotherapy and radiation, have been used with limited success. Bevacizumab is a recently described molecule, which inhibits endothelial proliferation and prevents formation of new blood vessels in tumor. However, this treatment confers increased hemorrhage risk and impairs wound healing. Therefore, the timing of surgery for patients receiving bevacizumab, who are in need of surgery, is critical. We performed a literature review to establish the appropriate timing between the cessation of bevacizumab therapy and surgical intervention. Our literature review indicated that the optimum time between cessation of bevacizumab therapy and surgery was 4 weeks. The timing for re-initiation of bevacizumab post-surgery was at least 2 weeks. The duration of preoperative cessation of bevacizumab treatment is critical in preventing life threatening surgical complications. The interval between the surgery and re-initiation of bevacizumab can be shortened. However, more studies are needed to ascertain the exact timing of preoperative and postoperative therapy.

1. Introduction

Glioblastoma multiforme (GBM), a Grade IV infiltrative glioma under the World Health Organization classification, is the most common primary brain tumor in adults and the deadliest subtype of glioma [1–3]. GBM incidence is approximately 10,000 [4] patients annually in the USA and longitudinal evidence suggests the number is increasing every year. It has an overall median survival of approximately 7 months from the time of diagnosis [3]. Commonly, survival and progression free survival have been the primary endpoints of clinical trials to date.

The current standard of care includes surgical resection followed by adjuvant radiotherapy and chemotherapy [5]. The extent of surgical resection is an independent risk factor for survival. One retrospective review showed that resection in excess of 98% of tumor volume yielded an increase in median survival from 8.8 to 13 months [5–7]. Although nitrosourea-based chemotherapy has historically produced only modest results in GBM, a phase III trial of temozolomide (TMZ; Temodar; Schering-Plough Corporation, Kenilworth, NJ, USA) utilized in combination with postoperative adjuvant radiotherapy demonstrated an increase in median survival from 12.1 to 14.6 months compared to patients receiving radiotherapy alone [8–10]. Despite therapeutic advances using molecular targeted therapies and immunotherapies, even the most aggressive clinical trials record a median survival for newly diagnosed GBM no higher than 19 months [5,6,8,10]. The recurrence rate is 100% for all treatment combinations, and 1 year survival in clinical trials of TMZ for recurrent GBM rarely exceed 35% [11]. Historically, phase II trials for a variety of chemotherapeutic regimens, including interferon-β, 13-cis-retinoic acid, carboplatin, procarbazine, and fluorouracil, have recorded, at best, a 9% combined response rate in these patients [12]. For this reason, there has been considerable focus into treatment alternatives for patients with recurrent GBM, for whom chemotherapeutic or radio-ablative options have already been exhausted.

Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) is a humanized anti-vascular endothelial growth factor

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http://dx.doi.org/10.1016/j.jocn.2014.05.054
0967-5868/

(anti-VEGF) immunoglobulin G monoclonal antibody that has yielded partial or complete response in 19.6 to 25.9% of patients with recurrent GBM who had already undergone surgery, radiotherapy, and TMZ treatment [13,14]. These results were demonstrated in two independent, randomized, prospective trials of bevacizumab for recurrent GBM [13], on the theoretical basis that GBM expresses a high level of membrane-bound VEGF [15,16]. Preventing angiogenesis in GBM may selectively inhibit its growth by inhibiting formation of new blood vessels. Based on these results, bevacizumab was granted accelerated approval by the USA Food and Drug Administration (FDA) in 2009 as a single-agent therapy for use in recurrent GBM refractory to prior chemotherapy or radiotherapy [13]. At the time of writing, bevacizumab is the only second line treatment for GBM, and it is the only agent approved for the treatment of recurrent high grade glioma. However, bevacizumab is not without risk. Major adverse effects experienced by patients on bevacizumab include intracranial hemorrhage, bowel perforation, cardiac failure, stroke, and wound dehiscence [14,17,18]. The increased risk of wound dehiscence, due to impaired angiogenesis, is an important surgical problem in these patients, creating a contraindication to re-operation until the antibody (with a half-life of 20 days) is cleared from circulation [19]. The drug manufacturer recommends postponing adjuvant initiation of bevacizumab for at least 4 weeks postoperatively and also recommends a 4 week delay after the discontinuation of neoadjuvant bevacizumab, before re-operation is attempted [18]. However, this recommendation possesses a serious ethical and technical dilemma for the neurosurgeon. The survival of patients who recur on bevacizumab is less than 4 months and to our knowledge only a few alternative treatments are possible without re-operation [20]. The majority of the new clinical immunotherapeutic trial enrollments require re-operation for histopathologic confirmation of diagnosis, debulking and tissue collection for the clinical trial. Given that GBM can double in size every couple of weeks, re-operating early can be a life-prolonging procedure for the patient. It is imperative that the optimal interval between surgical intervention and adjuvant bevacizumab discontinuation or initiation be clearly defined to allow for a safe and rapid surgery and postoperative initiation of chemotherapy. Beside the manufacturer's recommendations, there is no consensus in the literature on the optimal duration of this interval. This paper aims to provide an up-to-date review of the literature and the prevailing trends in the surgical community regarding the appropriate interval between halting bevacizumab therapy, re-operation and re-initiation of bevacizumab therapy.

An artist's impression of the mechanism of action of bevacizumab is shown in Figure 1.

2. Methods

A PubMed search was performed in April 2013 using the following keywords: Avastin, colorectal cancer, central port, bevacizumab, glioblastoma, dehiscence, wound healing, and VEGF. The objective was to review the current literature for retrospective studies and prospective trials examining the relationship between bevacizumab treatment and surgical intervention and postoperative wound complications, particularly in relation to timing of therapy.

3. Results

3.1. Bevacizumab and wound healing complications in general surgery

Bevacizumab was first approved by the FDA in 2004 for use in metastatic colorectal cancer (CRC). The only studies focused on the appropriate timing of surgery for patients on bevacizumab have been for CRC and central infusion port placement [21]. The association between bevacizumab use and wound dehiscence was well-recognized in CRC, with one retrospective study finding 9.1% of patients on bevacizumab experienced adverse events related to wound healing despite halting bevacizumab use 13 to 89 days preoperatively [22]. Hurwitz et al. concluded that CRC patients undergoing surgery after receiving bevacizumab were at elevated risk of wound healing and bleeding complications within 60 days after surgery [22]. August et al. documented five patients with colorectal anastomotic leakage following postsurgical administration of bevacizumab, reporting wound healing complications as late as 5 months to more than 1 year following surgery [23]. Other studies focusing on the use of bevacizumab in metastatic CRC found complication rates as high as 28% after a 7 week postoperative bevacizumab-free interval (adjuvant) and as low as 0% with a 5 week preoperative and postoperative bevacizumab-free interval (neoadjuvant and adjuvant) [24,25].

Some retrospective studies of wound healing complications in patients with central access ports receiving bevacizumab have demonstrated a temporal relationship between bevacizumab administration and wound healing complications, whereas one large prospective study found no significant relationship [26]. Erinjeri et al. performed a retrospective review of 1108 port placements in patients receiving bevacizumab and found that the risk of wound dehiscence in patients treated with bevacizumab was inversely proportional to the interval between bevacizumab administration and port placement [26]. They reported a relative risk of wound dehiscence of 8.1 ($p < 0.02$) if port placement occurred 1 day status-post bevacizumab injection and a relative risk of 11.5 ($p < 0.03$) if placement occurred within 7 days of bevacizumab injection, compared to patients not receiving bevacizumab [26]. There was no significant elevation of relative risk for an interval of 14 or 30 days [26]. Zawacki et al. reviewed 195 port placements in patients receiving bevacizumab and found 3.1% encountered wound dehiscence requiring port removal [27]. They reported a statistically significant difference in the interval between bevacizumab injection and port placement among those with dehiscence (10.8 days) compared to those without complication (16.9 days) [27]. They concluded that patients undergoing port placement within 11 days of bevacizumab therapy were at increased risk of wound dehiscence. In a prospective trial of fluorouracil, leucovorin, and oxaliplatin (FOLFOX6) with and without bevacizumab for patients with CRC, Allegra et al. noted abdominal incision and infusion port dehiscence in 1.7% of the 1332 patients enrolled in the bevacizumab treatment arm [21]. Despite a statistically significant difference in wound complication rates between the control and treatment sides of the study, they found no significant difference in the interval from surgical procedure to the initiation of bevacizumab between patients who developed a wound complication *versus* those who did not ($p = 0.88$) [21].

3.2. Bevacizumab and surgery for GBM

The literature discussing the subject of bevacizumab and intracranial surgery is far less voluminous than its colorectal counterpart due to the fact that bevacizumab is a relatively new drug for the treatment of GBM (received FDA approval for this application in 2009) and because of the relative rarity of GBM compared to CRC (Table 1). The original phase II studies evaluating the efficacy of bevacizumab alone and in combination with irinotecan chemotherapy 4 weeks after surgical resection demonstrated that craniotomy wound dehiscence and cerebrospinal fluid (CSF) leak were major complications of bevacizumab therapy [18,28]. Based on these results, and the estimated 20 day half-life of bevacizumab, the official package insert recommendation by Genentech was to postpone initiation of adjuvant bevacizumab treatment for 28 days

Table 1
Adjuvant bevacizumab and wound healing complications for glioblastoma multiforme reported in the literature

Author	Primary endpoint	Combination therapy	WHC	Use	Number of patients	Interval	WHC rate	Recommended interval
Gutin et al. [30]	Safety	HFSRT	Craniotomy dehiscence	Adjuvant	20	>4 weeks	0.050	–
Lai et al. [29]	OS	TMZ and RT	Wound infection and CNS hemorrhage	Adjuvant	70	3–6 weeks	0.071	>3 weeks
Narayana et al. [31]	OS	TMZ and RT	–	Adjuvant	15	>6 weeks	0	–
Narayana et al. [32]	OS	Irinotecan/ Carboplatin	CNS hemorrhage	Adjuvant	61	4 weeks	0.098	–
Vredenburgh et al. [33]	OS	Irinotecan	CNS hemorrhage	Adjuvant	35	>6 weeks	0.029	–
Friedman et al. [34]	PFS	Irinotecan/None	Craniotomy dehiscence and CNS hemorrhage	Adjuvant	167	>12 weeks, median 33 weeks	0.072	–
Chamberlain et al. [17]	PFS	Surgery/ Cyclophosphamide/ Erlotinib	Craniotomy dehiscence and CNS hemorrhage	Neoadjuvant/ Adjuvant	50	5–18 months; 4–6 weeks	0.08	–
Clark et al. [36]	Wound healing	Irinotecan/ Carboplatin/TMZ	Dehiscence, pseudomeningocele CSF leak, wound/bone infection	Adjuvant	18	<65 days	0.06	–
Clark et al. [36]	Wound healing	Irinotecan/ Carboplatin/TMZ	Dehiscence, pseudomeningocele CSF leak, wound/bone infection	Neoadjuvant	23	<65 days	0.35	4 weeks

CNS = central nervous system, CSF = cerebrospinal fluid, HFSRT = hypofractionated stereotactic radiotherapy, OS = overall survival, PFS = progression free survival, RT = radiotherapy, TMZ = temozolomide, WHC = wound healing complication.

status-post surgery [18] (Table 1). Lai et al. initiated a phase II study of bevacizumab plus TMZ and radiation therapy 3–6 weeks after surgical intervention. They reported one case of surgical-site central nervous system (CNS) hemorrhage and four cases of craniotomy-site wound infection among 70 enrolled patients [29]. They concluded that 3 weeks appeared to constitute a sufficient interval after craniotomy to initiate adjuvant bevacizumab with regard to the potential increase in CNS hemorrhagic events, but that bevacizumab treatment in the 3–6 week window likely increased the risk of wound infection, particularly in poorly healed wounds [29].

Most authors do not make recommendations regarding the proper interval between surgery and initiation of adjuvant bevacizumab. The literature reports a wide variation in timing among studies done on post-surgical patients treated with bevacizumab for recurrent GBM. Gutin et al. performed a prospective study to determine the safety of bevacizumab in combination with hypofractionated stereotactic radiotherapy on previously surgically treated and irradiated patients with recurrent GBM. They reported one case of craniotomy-site wound dehiscence among 20 enrolled patients, all of whom initiated therapy more than 4 weeks after surgery [30]. Narayana et al. performed two independent studies, finding CNS hemorrhage in 9.8% of 61 patients with an interval of 4 weeks before bevacizumab administration and no wound healing complications in 15 patients with an interval of at least 6 weeks after surgery before bevacizumab use [31,32]. Vredenburgh et al. also utilized a greater than 6 week interval for 35 patients with recurrent GBM on concomitant irinotecan and found CNS hemorrhage in 2.9% of patients [33]. In a large trial of 167 patients, Friedman et al. utilized a larger interval period of at least 12 weeks and still encountered a 7.2% incidence of wound healing complications, including craniotomy-site dehiscence and CNS hemorrhage [34].

Only a small minority of investigators, in the already small pool of literature, reported wound healing complications in patients who received bevacizumab as neoadjuvant therapy before surgical intervention. Chamberlain et al. performed a retrospective report of 50 patients receiving bevacizumab for recurrent GBM, 13 of whom underwent a repeat craniotomy after receiving bevacizumab [35]. The researchers did not report wound healing complications separately for these two populations however, and overall they reported an 8.0% incidence of wound dehiscence or CNS hemorrhage in their total study populations [35].

To our knowledge, Clark et al. performed the only retrospective study evaluating the safety of bevacizumab in patients who require re-operation after initiation of therapy [36]. They compared patients undergoing repeat craniotomy who were bevacizumab naïve, had received bevacizumab prior to reoperation, and received bevacizumab after repeat operation [36]. They found that patients receiving bevacizumab prior to surgery were significantly more likely to develop wound healing complications, including craniotomy-site dehiscence, pseudomeningocele, CSF leak, wound infection, and osteomyelitis [36]. Despite an interval period of at least 65 days, 35% of 23 patients who had previously received bevacizumab experienced wound healing complications [36]. Clark et al. recommended a 4 week interval at minimum between stopping bevacizumab and re-operating on these patients [36].

4. Discussion

The use of bevacizumab for the treatment of recurrent GBM and its direct impact on surgical complications is an active area of study. Most studies reviewed in this paper reported a 1–10% rate of complications in wound healing for patients receiving bevacizumab who had previously undergone craniotomy for tumor resection or biopsy [35,36]. These complications primarily included craniotomy-site dehiscence and CNS hemorrhage (Table 1) [35,36]. Most of these studies employed a 4–6 week window between surgical resection and initiation of bevacizumab, but some reported results after extremely long intervals, up to 5 months in one study (Table 1). There were similar rates of complications in most studies reviewed, indicating that there may be no interval at which the risk of wound site complication is eliminated for patients initiated on bevacizumab therapy. This notion is supported in the general surgery literature, which contains reports of wound dehiscence in CRC patients initiating bevacizumab therapy 1 year after surgical intervention [23]. Few recommendations exist for neurosurgeons and neuro-oncologists regarding the optimum timing of bevacizumab therapy after craniotomy. However, the consensus appears to be 4 weeks after surgery [14,18,35–37], which agrees with the manufacturer's recommendations.

The general surgery literature indicated that the interval of increased risk is greater for preoperative use of bevacizumab than postoperative use, when central infusion port dehiscence in patients on pre- or post-placement bevacizumab was evaluated [26,27].

During the early stages of wound healing, tissue regeneration relies heavily on angiogenesis for the reconstruction of the damaged capillary network and for the creation of a new capillary network [38]. Bevacizumab and other anti-VEGF antibodies interfere with wound healing by impairing neovascularization, hindering platelet-endothelial cell interaction, and reducing VEGF-induced tissue factor on endothelial cells [37,39]. The presence of anti-VEGF antibodies very early in the postoperative period, as with patients receiving bevacizumab prior to surgery, would be expected to interfere more significantly with wound closure than if bevacizumab was initiated after the critical period of capillary formation in the tissue.

The increasing use of bevacizumab in GBM patients is a concern for neurosurgeons, as nearly one in four patients with recurrent GBM are considered for repeat surgery [40,41]. GBM patients are currently receiving bevacizumab as first line therapy in combination with TMZ and radiation and also as second line agent for recurrent GBM. The question of when to operate after the discontinuation of bevacizumab has not received thorough investigation. To our knowledge, the only study evaluating the risk of wound healing complications in neurosurgical patients after use of bevacizumab was performed by Clark et al., which determined that a significantly increased risk of wound complications existed even after halting bevacizumab for 65 days [36]. The investigators concluded that neurosurgeons should delay re-operation for at least 4 weeks after discontinuing bevacizumab, in agreement with the recommendation of the drug manufacturer [18,36]. In 2009 Gordon et al. recommended delaying elective craniotomy for 6–8 weeks after treatment with bevacizumab [42].

The timing of surgery for recurrent GBM patients on bevacizumab has to be weighted not only against the risk of complications from surgery, but also against the rate of glioblastoma growth after bevacizumab treatment, and the risk of neurological disability or death without surgery and treatment. The literature reports that patient survival after progression on bevacizumab is less than 4 months [14,20]. Therefore waiting more than 4–6 weeks for re-operation would not be feasible.

With the advent of new anti-angiogenic agents, the timing of surgery becomes a very important clinical question. In the case of sunitinib, there is even more limited clinical experience regarding the timing of re-initiation of therapy following major surgical intervention. For example, the current recommendations state that the decision should be based on the clinical judgment and recovery from surgery.

5. Conclusions

Based on the results of our literature search, we feel that the postoperative interval for the initiation of bevacizumab treatment is not as critical as the preoperative interval. Evaluation of the postoperative use of bevacizumab in patients with recurrent GBM suggests that there is an increased risk of wound healing complications in these neurosurgical patients, but the effect is less pronounced than in the preoperative bevacizumab group. It appears that the critical period for capillary network formation is 2 weeks after the surgery [38]. Based on these data, it is reasonable to conclude that a study looking at initiation of bevacizumab 14 days after surgery in patients naïve to bevacizumab is warranted.

The literature also indicates that there is a more pronounced effect of preoperative bevacizumab on postoperative complications. In addition, the half-life of bevacizumab is reported to be 20 days. Therefore, based on the limited available data, we recommend a strict 4 week interval after discontinuation of bevacizumab therapy before surgical intervention. However, a study analyzing the optimal interval which balances the risk of complications and the risk of tumor progression should be undertaken.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2014.05.054.

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