

## Discontinuing Bevacizumab in Patients with Glioblastoma: An Ethical Analysis

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### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the considerations of beneficence, nonmaleficence, autonomy, and justice necessary to the care and counseling of patients with glioblastoma receiving treatment with bevacizumab.
2. Identify the ethical issues inherent to bevacizumab discontinuation in patients with glioblastoma whose tumors have progressed on the drug.



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### ABSTRACT

**Glioblastoma (GBM) is a highly lethal malignant brain tumor that expresses proangiogenic factors, including vascular endothelial growth factor (VEGF). Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), a monoclonal antibody against VEGF, is**

**routinely used in the U.S. to treat GBM patients whose tumors have progressed following initial therapy. The Ethics Advisory Committee at the Dana-Farber Cancer Institute was asked to provide consultation on two cases involving patients with recurrent GBM who were re-**

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ceiving bevacizumab. Despite evidence of disease progression, family members advocated for the continued use of bevacizumab because of its mild toxicity profile and concern that discontinuation would impair quality of life. However, continuing bevacizumab in this setting posed physical and financial risks to the patients and raised ethical concerns about resource allocation and justice.

We analyze the ethical questions regarding bevacizumab discontinuation in the setting of progressive GBM. We articulate the potential benefits and harms of continuing the drug and identify guiding principles for drug discontinuation that should be made transparent to patients and families. With the increasing availability of new, modestly toxic, expensive drugs for patients with advanced cancer, questions of when to stop these drugs will become increasingly relevant. *The Oncologist* 2011; 16:1435–1439

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## INTRODUCTION

Glioblastoma (GBM) is a highly lethal malignant brain tumor that expresses several proangiogenic factors, most importantly, vascular endothelial growth factor (VEGF) [1, 2]. Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), a monoclonal antibody to VEGF, is routinely used in the U.S. to treat patients whose GBMs have progressed following surgery, radiation therapy, and temozolomide. The Dana-Farber Cancer Institute Ethics Advisory Committee was asked to provide consultation regarding two patients with recurrent GBM who were receiving bevacizumab (Table 1). Despite evidence of disease progression, family members advocated for bevacizumab continuation, thereby raising ethical concerns. This paper explores whether continuation of bevacizumab after apparent progression of GBM can be justified by consideration of beneficence and nonmaleficence, and examines how other ethical principles such as autonomy and justice inform this decision.

## BEVACIZUMAB IN RECURRENT GBM

Folkman first hypothesized that antiangiogenic therapy could limit solid tumor growth [3]. This approach is now routinely used in the management of lung, colon, kidney, and brain cancer, among others. The chief driver of angiogenesis in human neoplasms is VEGF. Bevacizumab is a humanized monoclonal antibody against VEGF that was first approved by the U.S. Food and Drug Administration (FDA) in 2004 and received accelerated FDA approval for recurrent GBM in 2009.

The introduction of bevacizumab into the therapeutic armamentarium for recurrent GBM was an important advance, and several studies have indicated that the drug can benefit patients. Early retrospective studies found response rates of 25%–74%, far exceeding temozolomide's response rates of 5%–8% [4–6], and 6-month progression-free survival (PFS6) rates of 32%–64% [7–12], compared with a PFS6 rate of 21% for temozolomide [6]. These initial studies also showed a marked antiedema effect that permits dose reduction or even cessation of corticosteroids. The

first prospective phase II trial of bevacizumab and irinotecan yielded data consistent with the retrospective investigations [13, 14]. Two subsequent phase II trials in recurrent GBM patients led to bevacizumab's accelerated FDA approval. In the first, patients with recurrent GBM were treated with bevacizumab with or without irinotecan, yielding a response rate of 26% and PFS6 rate of 36% [1, 15]. The FDA also reviewed a phase II trial of bevacizumab monotherapy in 48 patients with recurrent GBM [16], reporting a 20% response rate [15].

## ETHICAL ANALYSIS

### Beneficence: The Hope of Benefit

Considerations of beneficence are an important reason to consider ongoing use of bevacizumab after GBM has progressed, because patients may derive benefits from the drug even after progression. These benefits may be physical, because bevacizumab may control peritumoral edema and neurological symptoms and decrease the need for steroids with their attendant toxicities [16, 17]. Moreover, stopping bevacizumab may lead to rapid clinical deterioration, perhaps secondary to rebound cerebral edema [2]. In addition, for some patients, continuing bevacizumab may provide psychological benefits. Mack et al. [18] recently showed that a minority of patients with advanced cancer desired attempts at life-extending therapy, even after recognizing the terminal nature of their disease. Although this subgroup of patients did not succeed in prolonging their lives, the authors note that some patients may nonetheless want assurance that they did “everything possible” to extend life.

Unfortunately, bevacizumab failure is inevitable and associated with poor outcomes. Although continuation of bevacizumab after tumor progression has been demonstrated to be of benefit in other contexts [19], its utility after GBM progression remains uncertain. Studies examining continuation of bevacizumab with a different chemotherapy agent demonstrate a very limited PFS interval [16, 20]. The low likelihood of further tumor control from bevacizumab provides a strong rationale for discontinuation of the drug in

**Table 1.** Summary of ethics consultations pertaining to bevacizumab

*Case #1:* An 84-year-old woman with a left frontal glioblastoma experienced disease progression despite temozolomide and radiation therapy. Approximately 3 months after beginning bevacizumab, she was noted to be dependent in all activities of daily living, to be incontinent in both urine and stool, and to be both nonverbal and lethargic during clinic visits. Although her physician recommended initiation of hospice services, her family members did not agree that the patient had deteriorated. They strongly advocated for bevacizumab to continue, believing the drug optimized her comfort and caused minimal side effects. On the other hand, the clinical team recommended discontinuation of bevacizumab, given the decline in the patient's function and the burden of travelling to clinic to receive a drug that no longer conferred benefit.

*Case #2:* A 38-year-old man with a glioblastoma diagnosed 12 months previously experienced growth of his tumor despite standard therapies. He received bevacizumab for several months but then experienced significant clinical decline. He became too weak to travel for drug administration, and his family members advocated for bevacizumab administration in his home. The patient rarely ate, drank, or voided, and had previously repeatedly expressed his desire to die at home. His wife, who was his health care proxy, believed that bevacizumab should be discontinued, but the patient's parents vigorously argued for ongoing treatment at home. The clinical team, who had not previously offered bevacizumab infusion at home, expressed concerns about both the safety and the ethics of such an intervention and of continuing the bevacizumab.

the setting of unambiguous tumor progression. In the two cases our ethics committee reviewed, patients and proxy decision makers facing this situation nevertheless requested that bevacizumab continue. In such cases, clinicians must explain clearly the limited potential for the patient to derive further benefit from bevacizumab.

### Nonmaleficence: Risk of Harm

Ethical analysis of the ongoing use of bevacizumab in the setting of progressive GBM must also acknowledge the risk for drug-related harm. Like other antiangiogenic therapies, bevacizumab is usually well tolerated. Hypertension, proteinuria, and fatigue are common and generally easily managed. Among 167 patients with recurrent high-grade gliomas who were treated with bevacizumab, there were only two serious intracranial hemorrhages [1, 15]. The incidence of venous thromboembolic events (8%) is similar to the general rate among patients with high-grade glioma [21]. Nevertheless, significant toxicities can occur with bevacizumab [16], and recent data indicate a higher treatment-related mortality rate in patients receiving the drug [22].

Beyond physical risks, patients taking bevacizumab despite clinical progression may experience financial harm. Insurance coverage for this drug may be incomplete such that the patient bears the burden of at least a portion of the drug's high cost [23]. When bevacizumab no longer controls the disease, this economic harm seem particularly difficult to justify. In addition, ongoing use of bevacizumab may preclude access to hospice services [24].

### Respect for Autonomy

Ethical decision making depends on integrating the clinicians' recommendations with the values and preferences of the autonomous patient. Physicians have a duty to respect and optimize each patient's right to self-determination. Respect for

autonomy, and its corollary obligation of informed consent, ethically requires that clinicians optimize communication with patients at the time of bevacizumab initiation so that patients understand the issues raised by discontinuing bevacizumab and the clinician's approach to these decisions. Whenever possible, health care proxies should be included in these discussions, because at the time that bevacizumab discontinuation because of GBM progression is considered, patients' decisional capacities may have deteriorated.

When a medical situation is ambiguous, and a clinician's recommendations uncertain, the importance of respecting the patient's autonomy is intensified. Clinical assessments about progression of GBM are often characterized by considerable uncertainty. Because bevacizumab reduces vascular permeability and therefore gadolinium extravasation, radiographic enhancement at the time of progression on bevacizumab may be lower than in patients treated with cytotoxic therapy. Furthermore, a subset of bevacizumab-treated patients demonstrate nonenhancing tumor progression seen only on T2-weighted and fluid-attenuated axial inversion recovery magnetic resonance imaging [12]. Measuring this greater signal intensity is challenging, and tumor growth may be mimicked by radiation-related changes, reductions in corticosteroid dosing, and other phenomena [25]. In the setting of clinical uncertainty, deference to patient preference has been recommended by consensus panels as optimally respecting patient autonomy [26].

The ethical obligation to optimize autonomy can come into conflict with the coexisting ethical obligation to maximize benefits while minimizing the risk for harm. Medical ethics has long recognized that respect for autonomy does not imply that patients have a right to request clinically inappropriate interventions [27]. When the balance of risks and benefits does not support an action requested by the patient, respect for autonomy is not sufficient to justify acqui-

escence by the clinician. This facet of the ethical analysis was pivotal to the ethics committee's recommendations regarding the two cases described here.

### Considerations of Justice

In light of bevacizumab's high cost, continuing the drug despite evidence of tumor progression raises ethical concerns for justice because the collective resources required might be better spent on other more effective treatments for individuals in other settings. This is particularly true in closed health care systems with fixed budgets, in which resources used by one patient imply less resources available to others. Justice considerations oblige health care systems, whether or not they have fixed budgets, to set ethical priorities that will increase efficiency, maintain fairness, and contain cost [28]. Yet Norman Daniels describes "unsolved rationing problems" that stem from a lack of agreement about how to distribute resources to achieve these goals [29]. Strech et al. [30] conducted a systematic review of the literature to clarify physicians' attitudes toward health care rationing. Acknowledging that some amount of health care rationing is inevitable, the authors highlighted significant ambivalence among physicians, who simultaneously endorsed setting limits on the use of health care resources but disliked explicit strategies for doing so [31]. Despite this ambivalence, physicians must routinely determine whether interventions requested by patients are worthwhile, and attention should therefore be paid to identifying the proper methods and processes for these determinations [32]. As in both these consultations regarding bevacizumab, physicians may be in a position to ration on the basis of a clinical opinion that the requested treatment may not bring sufficient benefits to justify the costs [32]. Clinical rationing in this way must be consistent, open, fair, and flexible enough to attend to relevant differences among individuals in order to maintain ethical justifiability and the public's trust [28, 32].

### RECOMMENDATIONS

These two ethically challenging cases highlight providers' obligations to communicate clearly with patients at the time of bevacizumab initiation. To optimize the balance of benefits and harms, patients should be informed not only of the physical risks of the drug but also of the potential for financial costs and restricted access to hospice services. Auton-

omous decision making is not possible unless these risks are disclosed. In addition, even though the threshold for stopping bevacizumab differs among patients, guiding principles for drug discontinuation should be made transparent to patients and their proxies upon the drug's initiation. Specifically, bevacizumab should be discontinued when disease progression, as evidenced by clinical deterioration clearly attributable to tumor progression, is convincingly demonstrated. Because there may be discordance between clinical status and neuroimaging, this recommendation holds whether or not radiographic progression accompanies the clinical decline [25]. We acknowledge that discontinuing bevacizumab in the absence of radiographic progression may be challenging, but it should nevertheless be seriously considered when the patient's clinical deterioration can only be explained by tumor progression. Conversely, in cases when a patient experiences clear radiographic progression but remains clinically stable with a good quality of life, bevacizumab may be justifiably continued.

The Ethics Advisory Committee recommended that the discontinuation of bevacizumab was ethically justifiable for both these patients. The physicians were not ethically obliged to continue the drug because the patients each exhibited clinical deterioration resulting from disease progression, and there was no evidence that continuing therapy would be efficacious. Moreover, the burdens of clinic visits were substantial for both patients, and drug continuation carried risks for harm. The balance of potential benefits and risks did not favor ongoing therapy with bevacizumab. In addition, in case 2, the committee emphasized the decision-making primacy of the health care proxy, who favored discontinuation. In both cases, bevacizumab was stopped.

As the availability of new, modestly toxic, expensive drugs for patients with advanced cancer grows, uncertainty about when to stop such drugs will become increasingly pressing [33]. Additional evidence and policy guidance are needed to guide clinicians, patients, and families as they confront these difficult questions.

### AUTHOR CONTRIBUTIONS

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