

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Bevacizumab for recurrent glioblastoma multiforme

Product: BEVACIZUMAB (Avastin®)

Class of Drugs: vascular endothelial growth factor (VEGF) inhibitor

Reason for Use: recurrent glioblastoma multiforme (GBM)

Manufacturer: Hoffmann-La Roche Limited

Date of Review: January 15, 2014

CED Recommendation

The CED recommended that bevacizumab (Avastin®), as a single-agent therapy, not be funded for the treatment of recurrent glioblastoma multiforme (GBM), on the basis that this treatment has not been proven to prolong survival, improve quality of life, or provide value for money.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided not to fund bevacizumab (Avastin®) for the treatment of recurrent glioblastoma multiforme (GBM).

Funding Status

Not funded through the Ontario Drug Benefit Program or the New Drug Funding Program (administered by Cancer Care Ontario) for this use.

Highlights of Recommendation:

- Bevacizumab can be used to treat various types of cancers. This funding review examined the use of bevacizumab in the treatment of glioblastoma multiforme (GBM), a type of brain cancer. In particular, the review assessed the use of bevacizumab, as a single-agent therapy, for recurrent GBM (i.e. disease that has worsened or progressed following initial therapy).
- The Committee to Evaluate Drugs (CED) previously assessed the funding of single-agent bevacizumab for recurrent GBM in 2010 and 2011. On both occasions, the CED recommended that bevacizumab not be funded in this setting because the treatment has not been proven to prolong survival and the clinical benefit compared to treatment cost (i.e., value for money) is unknown. (*For details, see: www.health.gov.on.ca/en/pro/programs/drugs/ced_rec_table.aspx.)*
- Hoffmann-La Roche made a funding resubmission for single-agent bevacizumab for the treatment of recurrent GBM in November 2013. An evaluation of this resubmission was undertaken by the Ontario Steering Committee of Cancer Drugs (OSCCD), with input from clinical experts who treat GBM. (*For details on the OSCCD, please see: www.cancercare.on.ca/toolbox/drugs/osccd/.)* The CED reviewed and agreed with the findings and recommendation of the OSCCD.
- The review considered only the funding of single-agent bevacizumab for recurrent GBM and focused on clinical trial data that have emerged since the last CED review in 2011. The funding of bevacizumab when used in combination with other treatments and the funding of first-line use of bevacizumab in GBM (prior to recurrence) were not considered.
- The BELOB trial provided the most relevant data for the evaluation. The study compared three treatment regimens in the recurrent GBM setting: single-agent bevacizumab, single-agent lomustine, and combination therapy with bevacizumab and lomustine. The study showed that the overall survival rate with single-agent bevacizumab was no better than that with single-agent lomustine. (The 9-month overall survival rate was 38% for single-agent bevacizumab compared to 43% for single-agent lomustine.) This was a phase II study and was not designed to show a difference in overall survival. However, combination treatment with bevacizumab and lomustine met the prespecified criterion for further investigation in clinical trials, whereas both drugs given as single agent failed to meet this criterion.
- In addition to the BELOB trial, the committee reviewed two clinical studies that were not directly related to the recurrent GBM setting but may add to the overall understanding of the efficacy of bevacizumab in treating this disease. The AVAglio and RTOG 0825 studies evaluated the use of bevacizumab as a first-line therapy, i.e., initial treatment for patients diagnosed with GBM. The two studies showed that the addition of bevacizumab to a current standard regimen (temozolomide-radiation) provided no improvement in overall survival.
- There is currently no conclusive clinical trial evidence to demonstrate that single-agent bevacizumab for the treatment of recurrent GBM improves quality of life.
- Bevacizumab costs approximately \$35,000 per patient for 9 cycles of treatment. The cost-effectiveness of this treatment remains uncertain.
- In summary, the committee noted that new clinical evidence did not convincingly show that single-agent bevacizumab improves overall survival or quality of life in patients with recurrent GBM. Furthermore, it is uncertain whether this treatment is cost-effective. For

these reasons, the committee recommended that single-agent bevacizumab not be funded in this setting.

Background:

Glioblastoma multiforme (GBM) is the most common and aggressive type of primary brain tumor. (Cancers that originate in the brain are known as primary brain tumors. These are different from secondary brain cancers, which originally developed elsewhere in the body and spread to the brain.) GBM develops from glial cells, which provide the structural backbone of the brain and support the function of neurons (nerve cells).

The most common symptoms of GBM are headache and seizures. Other symptoms include memory loss, muscle weakness, visual symptoms, difficulty in using or understanding language, and personality changes.

The prognosis for patients with GBM is poor. Treatments for GBM are directed at relieving symptoms and eliminating or reducing the size of the tumor. Common supportive therapies include corticosteroids to reduce the swelling of the brain and anticonvulsants to prevent seizures. Initial treatment options consist of surgery, radiation and/or chemotherapy.

Despite treatment, GBM reappears in most patients. There are currently no established standard therapies for recurrent GBM. Treatment options in this setting are limited and response rates are low with all existing therapies.

Bevacizumab belongs to a class of drugs called vascular endothelial growth factor (VEGF) inhibitors. It is thought to work by stopping the formation of blood vessels that bring oxygen and nutrients to tumors. Bevacizumab has received conditional market approval from Health Canada for use in patients with GBM who have relapsed or progressed after prior treatment. The approval was granted on the condition that confirmatory studies are conducted to verify its clinical benefit.

Detailed Discussions:

- This funding evaluation took into consideration:
 - Findings from the previous CED reviews, including the BRAIN study (*Friedman et al. Journal of Clinical Oncology 2009*) and the NCI 06-C-0064E study (*Kreisl et al. Journal of Clinical Oncology 2009*).
 - Clinical trials that have emerged since the 2011 funding review: the BELOB study, the AVAglio study, and the RTOG 0825 study (*all unpublished and available only in abstract*).
- The BELOB trial was a phase II, open-label, randomized study in 153 patients with recurrent GBM. The study compared single-agent bevacizumab, single-agent lomustine, and combination therapy with bevacizumab and lomustine. Study results showed that the 9-month overall survival rate was similar between single-agent bevacizumab and single-agent lomustine (38% and 43% respectively). This was a phase II study and was not designed to show a difference in overall survival. However, combination treatment with bevacizumab and lomustine met the prespecified criterion for further investigation in clinical trials, whereas both drugs given as single agent failed to meet this criterion.

- The AVAglio and RTOG 0825 were phase III placebo controlled studies evaluating the use of bevacizumab as a first-line treatment in patients with GBM prior to recurrence. The studies compared bevacizumab plus temozolomide-radiation to temozolomide-radiation without bevacizumab. Both studies failed to show an overall survival benefit with bevacizumab. The AVAglio study showed that bevacizumab provided a progression-free survival benefit of approximately four months, while the RTOG 0825 study did not show a progression-free survival benefit. With respect to quality of life, the AVAglio study suggested benefits on most of the quality of life domains, while the RTOG 0825 study showed neutral effects or potential detrimental effects on some domains.
- It was acknowledged that GBM is a debilitating disease and disease progression greatly impacts a patient's quality of life. There is no conclusive clinical trial evidence to demonstrate that single-agent bevacizumab improves quality of life in the recurrent GBM setting.
- With respect to toxicity, available studies suggest that the side-effects of bevacizumab in the treatment of GBM are likely similar to those seen with this drug in the treatment of other cancers.
- Bevacizumab costs approximately \$35,000 per patient for 9 cycles of treatment. The cost-effectiveness of this treatment remains uncertain.
- In summary, the committee noted that new clinical evidence did not convincingly show that single-agent bevacizumab improves overall survival or quality of life in patients with recurrent GBM. Furthermore, it is uncertain whether this treatment is cost-effective. For these reasons, the committee recommended that single-agent bevacizumab not be funded in this setting.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economics experts, and patients. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

Ontario Steering Committee for Cancer Drugs (OSCCD)

The OSCCD was created in 2013 to enhance and support the administration of Ontario's cancer drug programs. The committee advises the Ministry of Health and Long-Term Care's Ontario Public Drug Programs (OPDP) and Cancer Care Ontario's (CCO) Provincial Drug Reimbursement Programs.

The OSCCD's objective is to provide evidence-based clinical, health research and health economic guidance to the Executive Officer (EO) of OPDP on provincial cancer drug funding policies and decisions, program evaluation and drug-specific studies, and enhancements to cancer drug programs or initiatives in Ontario.

The OSCCD consists of members with expertise in oncology, hematology, pharmacy, pharmacology, health economics, and a patient representative.

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