

Bevacizumab for recurrent glioblastoma multiforme

Product:

BEVACIZUMAB (Avastin®)

Class of drugs:

vascular endothelial growth factor (VEGF) inhibitor

Indication:

Recurrent glioblastoma multiforme (GBM)

Manufacturer:

Hoffmann-La Roche Limited

Date of CED Review:

July 2010 & June 2011

CED Recommendation

The CED recommended that bevacizumab (Avastin®) not be funded for the treatment of recurrent glioblastoma multiforme (GBM), on the basis that this treatment has not been proven to improve survival.

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).

Status

Not funded through the Ontario Public Drug Programs.

Highlights of Recommendation:

- ◆ Bevacizumab can be used to treat various types of cancers. This 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 for recurrent GBM (i.e. disease that has relapsed or progressed following initial therapy).
- ◆ At present, there are no direct comparison studies between bevacizumab and alternative treatments to show that bevacizumab prolongs survival in patients with recurrent GBM.
- ◆ Existing evidence for the use of bevacizumab in recurrent GBM is largely made up of two studies in which all patients received bevacizumab. One of the primary measures used in the two studies was 6-month progression-free survival rate, which is defined as the percentage of patients alive and whose disease has not worsened at 24 weeks.
- ◆ The two studies showed that the use of bevacizumab in patients with recurrent GBM was associated with higher progression-free survival rates than those seen in historical studies.
- ◆ The committee noted that using historical estimates of survival as the basis for comparison is not reliable because treatment standards have evolved and historical rates are derived from studies that used older, less effective treatments. The committee questioned whether the suggested improvements in progression-free survival would translate into an improvement in overall survival.
- ◆ Based on existing evidence, the optimal therapy for patients with recurrent GBM remains unknown. Direct comparison studies are now underway to determine whether bevacizumab prolongs survival compared with other therapies in the first-line treatment of GBM. These studies may provide valuable information in the recurrent setting.
- ◆ With respect to side effects, the committee noted that the use of bevacizumab has been associated with increased bleeding risks, including intracranial bleeding.
- ◆ The average treatment cost for bevacizumab is approximately \$35,000 per patient (based on an estimate of 9 cycles of therapy). Value for money could not be established based on available information.
- ◆ Overall, the CED recommended that bevacizumab not be funded because it has not been proven to prolong survival in comparison to other existing treatment options and its value for money is unknown.

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 recurs in most patients. There are limited treatment options for patients with recurrent GBM, and response rates are low with 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.

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Detailed Discussion:

- ◆ The focus of the review was two phase II, open-label, non-comparative studies: 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). The two studies found that when compared with historical controls, the use of bevacizumab was associated with higher progression-free survival rates and disease response rates.
- ◆ The committee noted that indirect comparisons to historical controls are potentially biased, as older clinical studies did not use the current standard treatments such as temozolomide and chemoradiation therapy.
- ◆ There are currently no randomized controlled studies to indicate that bevacizumab provides a survival advantage over other alternatives in the treatment of recurrent GBM.
- ◆ It was noted that bevacizumab appears to stabilize the vasculature of the brain tumor. While this may spare the use of corticosteroids, it is uncertain whether bevacizumab does in fact have a true anti-tumor effect or whether it is simply acting in a similar manner as a corticosteroid.
- ◆ The committee noted that the optimal treatment for recurrent GBM has not been established. Moreover, the optimal timing and sequencing of the various available treatment options are unknown.
- ◆ A submission from a patient group was considered. The patient submission highlighted the burden of illness associated with GBM and the benefit of tumor shrinkage on cognitive and mobility functioning. The committee acknowledged that GBM is a devastating disease with a poor prognosis and limited treatment options.
- ◆ Bevacizumab costs approximately \$35,000 per patient for 9 cycles of treatment. The cost-effectiveness of this drug is unknown based on currently available information.
- ◆ **Overall, the CED recommended that bevacizumab not be funded because it has not been proven to prolong survival in comparison to other existing treatment options and its value for money is unknown.**

As part of this review, the CED took into consideration a submission provided by a patient group. (Details of the patient evidence submission process can be found at: www.health.gov.on.ca/english/providers/program/drugs/patient_evidence.html)

The CED worked jointly with a subcommittee involving cancer experts to review this cancer drug, as is done for all other cancer drug treatments.



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