Bevacizumab

Product:
BEVACIZUMAB (Avastin ®)

Class of drugs:
Anti-VEGF monoclonal antibody

Indication:
First-line treatment of metastatic colorectal cancer

Manufacturer:
Hoffman-LaRoche Limited

CED Recommendation

The CED recommended that bevacizumab (Avastin) not be funded through Cancer Care Ontario’s New Drug Funding Program for the treatment of metastatic colorectal cancer (mCRC). The CED acknowledged the clinical benefit of bevacizumab (Avastin) for this indication, but noted that, based on the submitted price, it does not represent good value-for-money in comparison to other funded cancer drugs, including other treatments for mCRC.

Executive Officer Decision

Taking into consideration the CED’s review and recommendation and based on a subsequent pricing agreement, the Executive Officer decided to fund bevacizumab (Avastin) through Cancer Care Ontario’s New Drug Funding Program, according to specific criteria.

Status

Funding is available through Cancer Care Ontario’s New Drug Funding Program.

Highlights of Recommendation:

- Bevacizumab (Avastin) is a VEGF inhibitor indicated for the first-line treatment of patients with metastatic cancer of the colon or rectum, in combination with fluoropyrimidine-based chemotherapy.
- Before bevacizumab (Avastin) became available, standard treatment for metastatic disease was combination chemotherapy using fluoropyrimidine, leucovorin and irinotecan (FOLFIRI regimen) or combination fluoropyrimide, leucovorin, oxaliplatin (FOLFOX regimen).
- Several studies showed that bevacizumab (Avastin) improves progression-free survival (the length of time during which a patient’s cancer does not worsen) in patients who have not previously received treatment for metastatic disease. One larger study, adding bevacizumab (Avastin) to the more common treatment regimen of fluoropyrimide / leucovorin / irinotecan, showed a statistically significant improvement in overall survival of 7.7 months compared to the regimen not including bevacizumab (Avastin).
- The clinical benefits of bevacizumab (Avastin) in patients whose disease has progressed despite previous chemotherapy requires confirmatory data, but the effect appears small (less than 2 months of improved survival).
- Bevacizumab (Avastin) can be associated with severe side effects, the most common being high blood pressure requiring drug treatment. Other less common but severe side effects include blood clots, bleeding, delayed wound healing and gastrointestinal perforation.
- At the submitted price, bevacizumab (Avastin) costs about $35,000 for one 10-month treatment course. Given the substantial number of patients who develop metastatic colorectal cancer (mCRC), the Committee indicated that the cost impact would be very significant if funded. Bevacizumab (Avastin) for mCRC is not a cost-effective treatment when it is compared to other funded treatments for this disease.
- Overall, the Committee acknowledged the clinical benefit of bevacizumab in the first line treatment of metastatic colorectal cancer but noted the high cost of funding. The Committee could only evaluate the cost-effectiveness of the treatment in the first line (previously untreated) setting and found the drug not cost-effective, particularly in relation to other funded cancer drugs. Therefore, the Committee recommended bevacizumab (Avastin) not be funded through Cancer Care Ontario’s New Drug Funding Program.

Background:

Colorectal cancer refers to cancer of the colon (large bowel) and cancer of the rectum. Metastatic colorectal cancer is colorectal cancer that has spread to other parts of the body, such as the liver and lung.

Only a small minority of patients can be cured with surgery once their cancer has spread to other organs. Combination chemotherapy (e.g. fluoropyrimidine, irinotecan, oxaliplatin), with or without bevacizumab, can be used to prolong survival. In most patients, resistance to chemotherapy develops over time.

Bevacizumab (Avastin) works by inhibiting the development of new blood vessels which a tumour requires in order to grow. This is specifically done by inhibiting vascular endothelial growth factor (VEGF), which is increased in metastatic disease. Bevacizumab is indicated for the first-line treatment of patients with metastatic carcinoma of the colon or rectum, in combination with fluoropyrimidine-based chemotherapy.

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Detailed Discussion:

- The CED reviewed two randomized, controlled studies of bevacizumab (Avastin) in the patients with previously untreated (first-line) metastatic colorectal cancer (mCRC) (Kabbinavar et al. J Clin Oncol 2003; Kabbinavar et al. J Clin Oncol 2005). In both studies, bevacizumab (Avastin) was given in addition to bolus fluorouracil / folinic acid combination, although in Ontario, the standard treatment is with infusional fluorouracil / folinic acid combined with irinotecan.
- In the first Kabbinavar study, patients given low dose (5mg/kg) bevacizumab (Avastin) had a median survival of 21.5 months compared to 13.8 months in the control group. Patients receiving bevacizumab (Avastin) also had a significantly longer median time until their cancer progressed (9 versus 5.2 months). A high-dose bevacizumab (10mg/kg) regimen was also studied and found to be inferior to the low dose regimen.
- In the second Kabbinavar study, patients on bevacizumab (Avastin) had a median survival of 16.6 months compared to 12.9 months in the control group. Patients receiving bevacizumab (Avastin) had a significantly longer time until their cancer progressed (9.2 versus 5.5 months).
- Neither Kabbinavar study had enough patients to determine if the additional survival benefits seen with bevacizumab (Avastin) were due to the treatment versus chance alone (i.e., they were not statistically powered to show a significant difference in overall survival).
- The CED also reviewed a large randomized controlled study, adding bevacizumab (Avastin) to irinotecan, fluorouracil and folinic acid, the most relevant study for the Ontario context (Hurwitz H et al. N Engl J Med 2004). This study demonstrated a significant difference is survival; 23.3 months in patients treated with bevacizumab (Avastin) versus 15.6 months in the control group. Progression free survival (that is the amount of time until a patient’s cancer progresses) was 10.6 months for patients receiving bevacizumab (Avastin) versus 6.2 months in the control group.
- One additional study of bevacizumab (Avastin) added to infusional fluorouracil, leucovorin and oxaliplatin (FOLFOX regimen) in patients whose disease had progressed on prior chemotherapy (i.e., the 2nd-line treatment setting) was briefly reviewed (Giannantonio et al. Proc Am Soc Oncol GI 2004). Although a modest survival advantage of 1.8 months was suggested, this study was only available in abstract form and full details were not available to assess the validity of the results. The Committee noted that once published, this study would be useful in assessing the strength of the evidence for bevacizumab (Avastin) in the second line setting.
- The main severe adverse effects reported in the clinical studies and subsequent post-market surveillance include hypertension (requiring drug treatment), blood clots including stroke and heart attack, bleeding (hemorrhage), delayed wound healing and gastrointestinal perforations. Congestive cardiac failure has also been reported.
- Bevacizumab (Avastin) costs approximately $35,000 per patient for a 10-month treatment course. Given the substantial number of patients that are affected by metastatic colorectal cancer, the Committee indicated that the cost impact of funding bevacizumab (Avastin) would be very significant.
- The manufacturer’s submitted cost-effectiveness analysis only addressed use of bevacizumab (Avastin) in the first line setting and did not include combination use with oxaliplatin based chemotherapy regimens. The submitted analysis suggests an incremental cost per quality adjusted life year (cost/ QALY) compared to an irinotecan/fluorouracil regimen that is roughly three times that seen for other cancer drugs. The CED concluded that bevacizumab (Avastin) in the first line setting was not cost-effective compared to other treatments for mCRC.
- Overall, the CED acknowledged the clinical benefit of bevacizumab (Avastin) in the first-line treatment of metastatic colorectal cancer but noted the high cost of funding. The Committee could only evaluate the cost-effectiveness of the treatment in the first line (previously untreated patient) setting and found the drug not cost-effective, particularly in relation to other funded cancer drugs.

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

Cancer Care Ontario Information:
Information on CCO chemotherapy regimens for metastatic colorectal cancer is available at: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=11562

The Gastrointestinal Disease Site Group Program in Evidence-Based Care Guideline for bevacizumab (Avastin) in colorectal cancer is available at: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10207

NDFP Criteria:
Bevacizumab (Avastin) is funded through Cancer Care Ontario’s New Drug Funding Program (NDFP) according to the following criteria:

- As combination therapy with the FOLFIRI regimen for first-line treatment of metastatic colorectal cancer.
- Dosing schedule: Avastin® 5mg/kg combined with the FOLFIRI regimen. Repeat every 14 days.
- Initial approval Period: 12 cycles

An additional four (4) cycles are funded for patient who meet the following criteria:
- Patient has initially met the NDFP eligibility criteria for using the first 12 cycles of Avastin® therapy;
- Completion of disease assessment by the treating oncologist at the 11th or 12th cycle of Avastin® is required, and must demonstrate either responding or stable disease in order for the patient to be eligible to receive up to a further 4 cycles of Avastin®. Acceptable staging tests include chest X-ray or CT scan of thorax for lung lesions and ultrasound or CT scan of abdomen for intra-abdominal lesions.
- Dosing schedule: Avastin® 5mg/kg combined with the FOLFIRI regimen. Repeat every 14 days.

For more information, please contact:
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