Summary

- Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF). It is thought that bevacizumab inhibits the formation of new blood vessels.

- Two clinical trials show that the addition of bevacizumab to a regimen of either fluorouracil plus leucovorin (FL) or FL combined with irinotecan (IFL) significantly improves response rate; and increases time to tumour progression and overall survival for patients with advanced colorectal cancer (ACC).

- Thromboembolic events are the most clinically significant adverse events, but hypertension, hemorrhage and gastrointestinal perforation are other potential safety concerns.

- More studies are needed to compare the combination of bevacizumab plus IFL to other chemotherapy regimens used in the treatment of ACC.

- The addition of bevacizumab to 5-fluorouracil-based chemotherapy regimens will significantly increase the costs of palliation for ACC.

The Technology

Bevacizumab is a recombinant humanized monoclonal antibody. It is thought to inhibit angiogenesis (the formation of new blood vessels) by binding to VEGF. It is unclear whether bevacizumab works by depriving cancer cells of their blood supply, thus reducing tumour cell growth; or whether it reverses the disorganized growth of tumour cells.

Regulatory Status

Bevacizumab has not been approved for use in Canada. In the US, the Food and Drug Administration (FDA) approved bevacizumab (Avastin™, Genentech, Inc., California) in February 2004 for use as first-line therapy, in combination with intravenous 5-fluorouracil-based chemotherapy, for the treatment of patients with metastatic cancer of the colon or rectum. Bevacizumab is undergoing pre-registration in the European Union.

Patient Group

In colorectal cancer, malignant tumours arise in the lining of the colon or rectum. Approximately 19,100 people in Canada will be newly diagnosed with colorectal cancer in 2004. Of these patients, 30% to 40% present with advanced colorectal cancer (ACC). Colorectal cancer ranks as the second leading cause of death from cancer in western countries and the third leading cause of cancer-related death worldwide.

Colorectal cancer is most commonly treated by surgical resection initially. For those with rectal cancer, initial treatment may also include pre- or post-operative radiation therapy. In Canada, up to 50% of patients who undergo potentially curative surgery relapse and die of advanced disease. Systemic chemotherapy has been shown to improve the survival of those who have undergone surgery and have evidence of advanced disease to the lymph nodes (stage III) at the time of surgery. Systemic chemotherapy is also used when colorectal cancer has spread to distant sites in the body. For most of these patients, treatment for widespread ACC is not curative.
Current Practice

For decades, chemotherapy for ACC was limited to regimens involving 5-fluorouracil alone or in combination with leucovorin. Without chemotherapy, the median duration of survival among patients was eight months. The addition of irinotecan to 5-fluorouracil plus leucovorin (IFL, also known as the Saltz regimen) significantly improved overall survival when it was compared to FL alone (median 14.8 months versus 12.6 months, p=0.04). The IFL regimen is now recommended as first-line therapy for patients with ACC. Oxaliplatin, which has been approved by the FDA for use as first- and second-line therapy in patients with ACC, is not approved for use in Canada. A commonly used combination of oxaliplatin and FL is called the FOLFOX regimen. Comparative studies of FOLFOX and Saltz regimens have shown that the former significantly improved overall survival rates (median 19.5 months versus 15.0 months; p=0.0001). In the US, oncologists are increasingly using the FOLFOX regimen as the standard of care for patients with ACC.

The Evidence

The addition of bevacizumab to intravenous 5-fluorouracil-based chemotherapy has been assessed in patients with ACC. Outcomes such as overall survival, progression-free survival, tumour response rate and duration of treatment response were evaluated.

In a randomized open-label phase II trial enrolling a total of 104 participants, the potential benefit and harm of bevacizumab given intravenously every two weeks in combination with FL chemotherapy were evaluated (Table 1). The results showed that treatment with FL-bevacizumab yielded better clinical outcomes.

<table>
<thead>
<tr>
<th>Phase II Trial¹⁵</th>
<th>Treatment</th>
<th>FL (n=36)</th>
<th>FL Plus Bevacizumab (5 mg/kg) (n=35)</th>
<th>FL Plus Bevacizumab (10 mg/kg) (n=33)</th>
<th>Pooled Hazard Ratio (from high and low doses for death or progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to disease progression in months (range)⁷</td>
<td>5.2 (0.2 to 11)</td>
<td>9.0 (0.6 to 11.5)</td>
<td>7.2 (0.7 to 12.7)</td>
<td>0.54</td>
<td></td>
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<tr>
<td>Tumour response rate (complete or partial)</td>
<td>6 (17%)</td>
<td>14 (40%)</td>
<td>8 (24%)</td>
<td>NR</td>
<td></td>
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<tr>
<td>Median duration of survival in months (range)⁸</td>
<td>13.8 (0.6 to 27.5)</td>
<td>21.5 (1.2 to 28.2)</td>
<td>16.1 (0.9 to 27.1)</td>
<td>0.86</td>
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<table>
<thead>
<tr>
<th>Phase III Trial¹⁶</th>
<th>Treatment</th>
<th>IFL-Placebo (n=411)</th>
<th>IFL-Bevacizumab (5 mg/kg) (n=402)</th>
<th>Hazard Ratio (for death or progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival in months</td>
<td>15.6</td>
<td>20.3</td>
<td>0.66</td>
<td></td>
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<tr>
<td>One-year survival rate (%)</td>
<td>63.4</td>
<td>74.3</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival in months</td>
<td>6.2</td>
<td>10.6</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>34.8</td>
<td>44.8</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>2.2</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>32.6</td>
<td>41.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of response in months</td>
<td>7.1</td>
<td>10.4</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

¹Primary outcome; ⁸secondary outcome; ⁷p values for all outcomes <0.01; FL=fluorouracil plus leucovorin; IFL=irinotecan, fluorouracil and leucovorin; NR=not reported.
at a lower dose (5 mg/kg) than at a higher dose (10 mg/kg). It is unknown whether this drug is effective at doses of <5 mg/kg.

In a randomized controlled phase III trial involving 813 patients with ACC, the combination of IFL plus bevacizumab improved survival compared with IFL plus placebo (Table 1). The chance of survival at 20.3 months was 50% in the IFL-bevacizumab group versus 38% in the IFL-placebo group. Thus, eight patients [95% confidence interval (CI): 5 to 19] would need to be treated with IFL-bevacizumab rather than IFL-placebo for one patient to be alive at 20.3 months follow-up. A similar result for progression-free survival is reported.

Results from another phase III trial comparing the FOLFOX regimen with or without bevacizumab (10 mg/kg) as second-line treatment are yet to be published. An interim analysis in 223 patients has shown that bevacizumab added to the FOLFOX regimen does not alter the toxicity profile associated with this regimen.

**Adverse Effects**

In the phase II trial, the rate of epistaxis (nosebleed) was significantly higher in the FL plus 5 mg/kg bevacizumab group compared with the FL-placebo group [risk difference (RD): 34%, 95% CI: 13 to 52]. In the phase III trial, the RD between IFL-bevacizumab versus IFL-placebo was 3% (95% CI: 0 to 2) for thrombotic events, 14% (95% CI: 9 to 19) for high blood pressure, 5% (95% CI: -0.2 to 1.1) for protein in the urine and 2% (95% CI: 0.0 to 5) for grade 3 or 4 bleeding. Gastro-intestinal perforations occurred in six patients (1.5%) receiving IFL-bevacizumab, but none were observed in the IFL-placebo group. In another trial published as an abstract, no significant effects on chemotherapy tolerability have been observed with the addition of bevacizumab to the IFL regimen.

Genentech, Inc. has issued an update on the serious adverse events related to the use of bevacizumab. The risk of a serious arterial thrombotic event (i.e., transient ischemic attack, stroke, myocardial infarction and angina) is approximately two-fold higher in patients receiving 5-fluorouracil-based chemotherapy plus bevacizumab, with an estimated overall rate of up to 5%. The risk of fatal arterial thrombotic events is also increased. These events occur more often in patients treated with bevacizumab who have a history of arterial thromboembolism before bevacizumab exposure and are ≥65 years old.

**Administration and Cost**

The average wholesale price of bevacizumab in the US is US$533.50 (100 mg vial) or US$2,134 (400 mg vial). The cost of therapy with bevacizumab for advanced colorectal cancer is US$44,000 to US$55,000 per patient over 10 months of treatment [i.e., 20 doses at 5 mg/kg (e.g. weight of 70 kg) every two weeks]. This is generally non-curative therapy. The Canadian price of bevacizumab is still unknown.

This cost will be in addition to an estimated US$42,000 for patients receiving the Saltz regimen or US$19,000 for patients receiving the FOLFOX regimen.

**Concurrent Developments**

A variety of small molecules that work inside blood vessel cells rather than attacking the VEGF receptor on the cell surface have been developed. These agents target an enzyme known as VEGF receptor tyrosine kinase. The most advanced is PKT787/ZK22845, an orally available agent that has been studied in phase III trials for treating colorectal cancer. The results of these trials are still unknown. Cetuximab (Erbilux™) is an antibody that targets the epidermal growth factor receptor, which is a molecule expressed on the surface of cancer cells in approximately 60% to 80% of patients with colorectal cancer. In February 2004, cetuximab was granted accelerated approval by the FDA for treating ACC, based on a favourable response rate in phase II trials.

**Rate of Technology Diffusion**

The high price of bevacizumab may discourage its use, given that FOLFOX leads to similar
survival benefits as those from the bevacizumab plus Saltz regimen, but at a lower cost.14

The FDA approved a broad indication for the use of bevacizumab (i.e., in combination with any 5-fluorouracil-based chemotherapy regimen when given as first-line therapy that is not limited to IFL). Thus, bevacizumab may be prescribed for most patients with ACC. Its indication in Canada will determine its projected rate of diffusion.

Bevacizumab is also being evaluated in multiple tumour types such as renal cell carcinoma, advanced non-small cell lung cancer, locally advanced pancreatic cancer and metastatic breast cancer.1 No approval has been granted for using bevacizumab for such diseases.1

Implementation Issues

The available results apply to patients with ACC who have not been previously treated. Bevacizumab’s effect on ACC that is refractory to standard therapies is being explored.1

Other clinical trials show that the FOLFOX regimen produces similar survival benefits compared to IFL plus bevacizumab. FOLFOX is being used as the standard therapy for colorectal cancer patients in the US.7 Thus, to determine the optimal role of bevacizumab in colorectal cancer therapy and to define the optimal dosage, schedule of administration and management of toxicities, further studies are needed.23

The addition of bevacizumab to existing colorectal cancer regimens will significantly increase treatment costs. In deciding whether to provide funding for this agent, an economic evaluation should be considered.

References


Cite as: Hadj Tahrar A. Bevacizumab for advanced colorectal cancer [Issues in emerging health technologies issue 63]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2004. 

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CCOHTA takes sole responsibility for this bulletin and appreciates comments from its reviewers.

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*Dr. Goldberg served as a consultant to Genentech and received honoraria for that activity.