Cost-effectiveness analysis of bevacizumab combined with chemotherapy for the treatment of metastatic colorectal cancer in Japan
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study investigated the treatment of metastatic colorectal cancer (mCRC) with bevacizumab plus chemotherapy versus chemotherapy alone. The chemotherapy regimens investigated were:

- irinotecan/5-fluorouracil/leucovorin (IFL);
- 5-fluorouracil/leucovorin (FU/LV);
- infusional 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX);
- bolus 5-fluorouracil/leucovorin/oxaliplatin (bFOL);
- capecitabine/oxaliplatin (CAPOX); and
- second-line FOLFOX.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis

Study population
The study population comprised a hypothetical cohort of mCRC patients in Japan.

Setting
The study setting was secondary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2007. The price year was 2006.

Modelling
Owing to the limited time horizons of trials, survival data were extrapolated using a Weibull regression model.

Study designs and other criteria for inclusion in the review
The main clinical data used in the economic evaluation were progression-free survival, disease-free survival and overall survival.

Sources searched to identify primary studies
The clinical effectiveness data were derived from six published randomised controlled trials.

Methods used to derive estimates of effectiveness
The authors reported that a review of the literature had been undertaken by searching MEDLINE, UpToDate and...
American Society of Clinical Oncology (ASCO) Virtual meeting. MEDLINE was searched using the following strategy: bevacizumab limited to randomised controlled trial. Only randomised controlled trials were included in the review. It was unclear whether or how the results of these trials were combined.

**Measure of benefits used in the economic analysis**
The measure of benefits used was the life-years gained. Discounting was relevant since benefits were generated over the lifetime of the patient, but it was not performed.

**Direct costs**
The direct costs to the health care payer were considered in the analysis. These included the costs of bevacizumab, chemotherapy, other supportive medications, routine follow-up, diagnostic imaging, blood tests and infusion pump. The authors reported that resource use was based on the dose and schedule for each treatment under study. The unit costs were derived from per-unit drug tariffs and reimbursement schedules. The authors did not report the time horizon over which the costs could be incurred and, consequently, it is unclear whether the costs should have been discounted. The authors reported the incremental costs of bevacizumab plus chemotherapy compared with chemotherapy alone. The price year was 2006.

**Statistical analysis of costs**
Incremental mean costs were reported alongside their 95% confidence intervals (CIs).

**Indirect Costs**
Productivity costs were not included.

**Currency**
Japanese yen (JPY).

**Sensitivity analysis**
A series of one-way sensitivity analyses was undertaken by varying the model parameters. In addition, a probabilistic sensitivity analysis was performed in order to determine the robustness of the results. For cost data, the authors assumed normal distributions.

**Estimated benefits used in the economic analysis**
The incremental benefits of bevacizumab plus chemotherapy compared with chemotherapy alone were:

- for bevacizumab+IFL versus IFL, 0.40 (95% CI: 0.17 to 0.63);
- for bevacizumab+FU/LV versus FU/LV, 0.13 (95% CI: -0.28 to 0.50);
- for bevacizumab+FOLFOX versus FOLFOX, 0.27 (95% CI: -0.32 to 0.86);
- for bevacizumab+bFOL versus bFOL, 0.27 (95% CI: -0.34 to 0.88);
- for bevacizumab+CAPOX versus CAPOX, 0.86 (95% CI: 0.08 to 1.64);
- for bevacizumab+second-line FOLFOX versus second-line FOLFOX, 0.17 (95% CI: 0.07 to 0.43).

**Cost results**
The incremental mean costs (in million JPY) of bevacizumab plus chemotherapy compared with chemotherapy alone were:

- for bevacizumab+IFL versus IFL, 4.8 (95% CI: 2.9 to 7.6);
- for bevacizumab+FU/LV versus FU/LV, 2.2 (95% CI: -0.2 to 5.3);
- for bevacizumab+FOLFOX versus FOLFOX, 3.7 (95% CI: 0.4 to 8.2);
for bevacizumab+bFOL versus bFOL, 4.6 (95% CI: 0.1 to 8.0);
for bevacizumab+CAPOX versus CAPOX, 7.4 (95% CI: 3.0 to 12.9);
for bevacizumab+second-line FOLFOX versus second-line FOLFOX, 3.6 (95% CI: 2.0 to 5.6).

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (ICER; i.e. the additional cost per life-year gained. The ICERs of bevacizumab plus chemotherapy compared with chemotherapy alone were:

for bevacizumab+IFL versus IFL, JPY 11.9 million;
for bevacizumab+FU/LV versus FU/LV, JPY 17.4 million;
for bevacizumab+FOLFOX versus FOLFOX, JPY 13.5 million;
for bevacizumab+bFOL versus bFOL, JPY 16.9 million;
for bevacizumab+CAPOX versus CAPOX, JPY 8.5 million;
for bevacizumab+second-line FOLFOX versus second-line FOLFOX, JPY 14.1 million.

The authors reported that the sensitivity analyses showed the ICERs to be insensitive to changes in palliative costs.

The results of the probabilistic sensitivity analyses showed that the probability that the ICER of additional bevacizumab was below JPY 10 million ranged from 5 to 63%, depending on the chemotherapy agent.

**Authors' conclusions**
The authors concluded that the incremental cost-effectiveness ratios (ICERs) of bevacizumab plus FU/LV (5-fluorouracil/leucovorin) combination treatment, IFL (irinotecan/5-fluorouracil/leucovorin), and second-line FOLFOX (infusional FU/LV/oxaliplatin) were high in comparison with other chemotherapies for metastatic colorectal cancer (mCRC). The authors also considered that no final conclusions could be drawn until the results of an ongoing large trial were published.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using chemotherapy as the comparator. It represented current practice in the authors’ settings. You should decide if the chemotherapy treatments used in this study represent current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The parameters were derived from published research, but it was unclear whether any synthesis of the study results took place since the authors reported no details of this in their methods section. The authors appropriately reported the sources used to identify relevant studies, and the search strategy used, and also reported the results of their review.

**Validity of estimate of measure of benefit**
The estimation of health benefit (life-years gained) was derived appropriately using a Weibull regression model. The benefits were not discounted, even though this would have been relevant.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the health care payer paying for the treatment. Given this perspective, it appears that all the relevant categories of costs have been included in the analysis. However, the authors did not provide sufficient details of the resource use categories included and, consequently, it is unclear if all relevant costs were included. Furthermore, it is unclear how the authors estimated or derived resource use. It would appear that charges were used to proxy prices, which was appropriate given the payer perspective of the study.
authors did not report the time horizon over which the costs were incurred, thus it is unclear whether or not discounting was relevant. The price year was reported, which will aid any further inflation exercises.

Other issues
The authors reported that their findings were in line with those observed by the National Institute for Health and Clinical Excellence. The issue of generalisability was partly addressed in the sensitivity analyses. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of their analysis. The authors acknowledged a number of further limitations to their study. In particular, they did not use quality-adjusted life-years as their measure of health benefit, and the study did not consider indirect costs or costs borne by patients or their families.

Implications of the study
The authors reported that further information is needed to assess the cost-effectiveness of first-line bevacizumab with oxaliplatin.

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