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Title **Systematic Review and Economic Evaluation of Bevacizumab and Cetuximab for the Treatment of Metastatic Colorectal Cancer**

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Aim

To assess the clinical and cost effectiveness of bevacizumab and cetuximab in treating metastatic colorectal cancer (CRC).

Conclusions and results

Adding bevacizumab to irinotecan in combination with 5-FU/folic acid (FA) + irinotecan resulted in a statistically significant increase in median overall survival (OS) of 4.7 months. Adding bevacizumab to 5-FU/FA resulted in a nonsignificant increase in median OS of 3.7 months in one study and 7.7 months in another. Adding bevacizumab to irinotecan, fluorouracil, and leucovorin (IFL) resulted in a statistically significant increase in median progression-free survival (PFS) of 4.4 months. Adding bevacizumab to 5-FU/FA resulted in a statistically significant increase in median PFS of 3.7 months, and a statistically significant increase in time to disease progression of 3.8 months. An overall tumor response rate of 44.8% was reported for bevacizumab + IFL compared to 34.8% for IFL + placebo. This improvement in tumor response was statistically significant. Adding bevacizumab to 5-FU/FA resulted in a significant difference in tumor response rate in one study, but not another. Bevacizumab combined with IFL or 5-FU/FA resulted in an increase of grade 3/4 adverse events. Economic assessment suggests that the cost effectiveness of bevacizumab + IFL is unlikely to be better than GBP 46 853 per life-year gained (LYG); the cost-utility of bevacizumab + IFL is unlikely to be better than GBP 62 857 per quality-adjusted life-year (QALY) gained. The cost effectiveness of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 84 607 per LYG; the cost-utility of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 88 658 per QALY gained.

No trials met the inclusion criteria for the systematic review of cetuximab. A Phase II trial reported a median OS duration of 8.6 months for patients receiving cetuximab + irinotecan, and suggested that treatment with cetuximab combined with irinotecan is associated with significantly more adverse events than cetuximab monotherapy. A single arm study of cetuximab + irinotecan reported a median OS duration of 8.4 months, a median time to progression of 2.9 months and a tumor response rate of 15.2%. The cost-effectiveness model suggested that the expected survival duration of patients receiving cetuximab + irinotecan is 0.79 years. For cetuximab + irinotecan to achieve a cost-utility ratio of GBP 30 000 per QALY gained, treatment must provide an additional 0.65 life years over treatment with active/best supportive care.

Recommendations

Trials indicate that bevacizumab combined with 5-FU/FA and bevacizumab combined with IFL are clinically effective in comparison with standard chemotherapy options in first-line treatment of metastatic CRC. Economic analysis suggests that the marginal cost-utility of bevacizumab + IFL versus IFL is unlikely to be better than GBP 62 857 per QALY gained, and the marginal cost-utility of bevacizumab + 5-FU/FA versus 5-FU/FA is unlikely to be better than GBP 88 658 per QALY gained. No evidence shows whether cetuximab combined with irinotecan improves health-related quality of life (HRQoL) or OS in comparison with active/best supportive care or oxaliplatin + 5-FU/FA. Indirect comparisons suggest that the incremental cost-utility of cetuximab + irinotecan is unlikely to be better than GBP 30 000 per QALY gained.

Methods

See Executive Summary link above.

Further research/reviews required

Examples of further research needed:

- clarify the true impact of first-line bevacizumab combined with irinotecan and/or infusional 5-FU/FA on OS in patients with metastatic CRC
- study the optimal role of bevacizumab alongside oxaliplatin, irinotecan and 5-FU/FA
- investigate (RCT) the impact of bevacizumab treatment on HRQoL
- study the resource implications associated with bevacizumab
- compare the impact of cetuximab + irinotecan to active/best supportive care

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