Oxaliplatin and capecitabine for the adjuvant treatment of colon cancer

The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation

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Executive summary

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Executive summary

Background

In the UK, about 26% of patients diagnosed with colorectal cancer are classified as Stage III (Dukes' C) at presentation. These patients have an overall 5-year survival rate of between 25 and 60%. After a complete surgical resection (undertaken with curative intent), stage III patients with colon cancer have a 50–60% chance of developing recurrent disease. Adjuvant chemotherapy is given after surgery to eliminate any occult micro-metastases that might be present and decrease the incidence of disease recurrence, offering colon cancer patients increased potential for cure.

The management of colorectal cancer is constantly evolving. The administration of 6–7 months of 5-fluorouracil/leucovorin (5-FU/LV) has until recently been considered standard treatment for patients with Stage III (Dukes' C) colon cancer, after curative surgical resection. The most widely used adjuvant treatment schedule in England and Wales is the weekly bolus QUASAR 5-FU/LV regimen given for 30 weeks; however, there remains significant geographical variation in the 5-FU-based regimens currently in use in the UK.

Objectives

The objectives were to assess the clinical and cost-effectiveness of oxaliplatin in combination with 5-FU/LV, and capecitabine monotherapy (within their licensed indications), as adjuvant therapies in the treatment of patients with Stage III (Dukes' C) colon cancer after complete surgical resection of the primary tumour, as compared with adjuvant chemotherapy with an established fluorouracil-containing regimen.

Methods

In all, 10 electronic databases were searched up to January 2005 and over 30 health technology assessment and cancer-related organisations were consulted via the World Wide Web. The sponsor and other submissions of evidence to the National Institute for Health and Clinical Excellence (NICE) and the reference lists of key papers were hand-searched. The extracted data and quality assessment variables were presented for each study. In addition, results of eligible studies were statistically synthesised (meta-analysed) where appropriate.

A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact on health-related quality of life. Probabilistic sensitivity analysis was used to generate information on the likelihood that each of the interventions was optimal.

Results

Number and quality of studies

Of the 1499 titles and abstracts screened, 88 full papers were retrieved and assessed in detail. Three Phase III randomised controlled trials of varying methodological quality were included in the review.

Summary of benefits and risk

Oxaliplatin used in combination with 5-FU/LV

The evidence to support the addition of oxaliplatin to adjuvant treatment is at present limited to two large trials – the MOSAIC trial and NSABP C-07 study. The MOSAIC trial, a large (n = 2246), international, multi-centre, Phase III, randomised, open-label, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4 regimen) or infusional 5-FU/LV alone (the de Gramont or LV5FU2 regimen) for 6 months in patients with Stage II (40%) or III (60%) colon cancer. The primary trial end-point was disease-free survival. Secondary trial end-points included toxicity and overall survival. The NSABP C-07 study, a large (n = 2492), international, multi-institution, Phase III, randomised, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with a bolus Roswell Park schedule of 5-FU/LV (FLOX regimen) or bolus 5-FU/LV alone (Roswell Park regimen) for 24 weeks in patients with Stage II (29%) or III (71%) colon cancer. The primary and secondary trial end-points were similar to those in the MOSAIC trial. No data were reported on quality of life in either trial. ▶

Subgroup analyses by disease stage in the MOSAIC trial (data not reported for the NSABP C-07 study) showed that in patients with Stage III (any T, N1 or N2, M0) colon cancer the probability of remaining disease-free at 3 years was 72.2% and 65.3% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. For the intention-to-treat (ITT) population, the hazard ratio for recurrence was 0.76 (95% CI: 0.62 to 0.92; p = significant), corresponding to a 24% reduction in the risk of relapse or death and an absolute disease-free survival difference of 6.9% and a number needed to treat of 14.2 (95% CI: 8.7 to 44.2) to produce one additional patient who remains alive and disease-free at just over 3 years by using FOLFOX4 instead of infusional 5-FU/LV alone (de Gramont regimen) as adjuvant chemotherapy. These results are similar to those for the overall population of the MOSAIC trial (hazard ratio using ITT analysis, 0.77; 95% CI: 0.65 to 0.91; $p = 0.002$) and the NSABP C-07 study (hazard ratio using per protocol analysis, 0.79; 95% CI: 0.67 to 0.93; $p < 0.004$).

Updated subgroup analyses (not specified in the trial protocol) showed that the benefit observed at 3 years in patients with Stage III colon cancer was maintained and improved with longer follow-up. The probability of disease-free survival at 4 years was 69.7% and 61.0% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. The hazard ratio for recurrence for the ITT population was 0.75 (95% CI: 0.62 to 0.90; $p = 0.002$) with an absolute disease-free survival difference of 8.7% and a number-needed-to-treat of 12.5 (95% CI: 7.9 to 32.4).

The overall results of the MOSAIC trial (patients with Stage II and III colon cancer) showed that the frequency of severe (grade 3 or 4) paraesthesia, neutropenia, diarrhoea, nausea, vomiting and thrombocytopenia were significantly ($p < 0.001$) more pronounced with oxaliplatin plus infusional 5-FU/LV than with infusional 5-FU/LV alone. Similarly, in the NSABP C-07 study, diarrhoea and paraesthesia were more common with oxaliplatin plus bolus 5-FU/LV than with bolus 5-FU/LV alone (p-values not reported). The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen), which, although significant and frequent (all-grade neurotoxicity, >85%; grade 3 neurotoxicity, >8%), does appear to improve within 1 year's time for the majority of patients (grade 3 neurotoxicity, <1.1%). However, approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment.

Capecitabine

The evidence to support the use of oral capecitabine as adjuvant treatment is at present limited to the X-ACT study, a large (n = 1987), international, multi-centre, Phase III, randomised, open-label, active-controlled trial. This trial compared oral capecitabine (eight cycles) with a bolus Mayo Clinic regimen of 5-FU/LV (six cycles) for a total of 24 weeks in patients with Stage III (Dukes' C) colon cancer. The primary trial end-point was at least equivalence in disease-free survival. Secondary trial end-points included relapse-free survival, overall survival, safety and quality of life. It should be noted that the Mayo Clinic regimen, although internationally accepted as a reference regimen, is not commonly used in the UK, where it is widely regarded as producing an unacceptably high rate of toxicity.

Capecitabine therapy was shown to be at least equivalent to 5-FU/LV, in that the primary end-point was met [upper limit of the 95% CI of the hazard ratio was significantly ($p < 0.001$) below both predefined margins of 1.25 and 1.20 for at least equivalence]. At 3 years (pre-specified analysis), the probability of remaining disease-free was 64.2% and 60.6% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.87 (95% CI: 0.75 to 1.00; $p = 0.05$ for superiority) corresponding to a 13% reduction in the risk of relapse/death and an absolute disease-free survival difference of 3.6%. Updated results (analysis not pre-specified) with a median follow-up of 4.4 years (with minimum follow-up of 3 years for all patients) confirm the earlier results and demonstrate that capecitabine is equivalent to 5-FU/LV (hazard ratio of 0.87; 95% CI: 0.76 to 1.00; $p = 0.055$ for superiority).

Capecitabine therapy improved relapse-free survival. At 3 years (pre-specified analysis), the probability of remaining relapse-free was 65.5% and 61.9% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.86 (95% CI: 0.74 to 0.99; $p = 0.04$ for superiority), corresponding to a 14% reduction in the risk of relapse/death and an absolute relapse-free survival difference of 3.6%. Updated results (analysis not pre-specified in the protocol) with a median follow-up of 4.4 years showed a trend in favour of capecitabine (hazard ratio of 0.87; 95% CI: 0.75 to 1.00; $p = 0.057$ for superiority).

▶

There were no major (statistically significant) differences in quality of life between oral capecitabine and 5-FU/LV from baseline to 25 weeks of trial treatment (no statistical data reported); however, other studies suggest that patients prefer oral chemotherapy to intravenous treatment.

As a result of toxicity, both groups required dose modifications, interruptions and delays (capecitabine 57% versus 5-FU/LV 52%). Adverse events most commonly leading to dose modifications (including treatment interruption and dose reduction) were hand–foot syndrome (31%) and diarrhoea (15%) in the capecitabine group and stomatitis (23%) and diarrhoea (19%) in the 5-FU/LV group. The frequency of severe (grade 3 or 4) stomatitis (2 versus 14%; $p < 0.001$) and alopecia (0 versus <1%; $p < 0.02$) was significantly less common in capecitabine-treated patients than in those receiving 5-FU/LV. The incidence of neutropenia as a grade 3 or 4 laboratory abnormality was significantly ($p < 0.001$) lower in the capecitabine group (2%) than in the 5-FU/LV group (26%). Grade 3 hand–foot syndrome was the only severe adverse event occurring more often with capecitabine than 5-FU/LV (17 versus <1%; $p < 0.0001$, respectively).

Other evidence

Infusional 5-FU/LV adjuvant-based therapy is equivalent to, but with relatively less toxicity than, bolus 5-FU/LV in extending survival and a better quality of life. The major drawbacks of continuous infusion with 5-FU are catheter-associated complications and its adverse effects.

Summary of cost-effectiveness

The independent economic analysis used a state transition (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 50 years post-surgery. This included the use of economic modelling from a recent NICE assessment of chemotherapies for advanced colorectal cancer. The primary outcome of interest in this assessment was the cost per quality-adjusted life-year (QALY) gained, associated with capecitabine and oxaliplatin (in combination with 5-FU/LV). The economic model uses survival analysis techniques to predict long-term survival, therefore assuming that the short-term survival differences observed within the trials are translated into long-term benefits.

With this important proviso, the results of the cost-effectiveness results estimate that capecitabine is a dominating strategy over a 50-year time horizon when compared with the Mayo Clinic 5-FU/LV regimen, saving an average of approximately £3320 per patient. Capecitabine is estimated to improve survival outcomes over the entire 50-year period, through extrapolation of the survival estimates observed in the trial to date. Over the same 50-year period, oxaliplatin in combination with 5-FU/LV (FOLFOX4 regimen) is estimated to cost an additional £2970 per QALY gained when compared with the de Gramont 5-FU/LV regimen, a figure well below the cost-effectiveness ratio of many health interventions currently available on the NHS.

The one-way sensitivity analyses demonstrated that the costs and QALY gains associated with both therapies are driven by the long-term survival of patients who do not relapse. The results of the probabilistic sensitivity analyses demonstrate the robustness of the central estimates of cost-effectiveness. Capecitabine was consistently found to be a dominating intervention when compared with 5-FU/LV. Oxaliplatin (in combination with 5-FU/LV) demonstrated superior survival outcomes, with marginal costs, when compared with the de Gramont 5-FU/LV regimen. Based upon the assumptions made in the economic model, the cost-effectiveness acceptability curves demonstrate that the two interventions have a high probability of being cost-effective at thresholds of both £20,000 and £30,000, when compared with the 5-FU/LV comparator arms in the two trials.

An indirect comparison of the FOLFOX4 and Mayo Clinic 5-FU/LV regimens (using data from both the MOSAIC and X-ACT studies) suggests that the use of FOLFOX4 in place of the standard Mayo Clinic 5-FU/LV regimen would cost an additional £5777 per QALY gained.

Furthermore, an additional indirect comparison demonstrated that there is considerable uncertainty regarding the incremental cost-effectiveness of FOLFOX4 when compared with capecitabine. Using the extrapolated effectiveness data from the trials and the estimated costs of each intervention to inform this comparison suggests an incremental cost-effectiveness ratio of approximately £13,000 per QALY gained from treatment with FOLFOX4, compared with capecitabine. However, if it is assumed that the Mayo Clinic and the de Gramont 5-FU/LV regimens are equivalent in terms of effectiveness (and therefore using the marginal QALY gains of the two interventions against their 5-FU/LV comparators), the analysis estimates that the ICER

of FOLFOX4 in comparison with capecitabine may be greater than £30,000 per QALY. There is therefore considerable uncertainty in this comparison, owing to the differences in long-term survival predicted in the 5-FU/LV regimens in the two trials.

Conclusions

Clinical effectiveness

Evidence from the MOSAIC trial demonstrated that oxaliplatin (in combination with 5-FU/LV) therapy was more effective in preventing or delaying disease recurrence than 5-FU/LV alone in the adjuvant treatment of patients who had undergone complete surgical resection for Stage III colon cancer (data not reported separately for Stage III patients in the NSABP C-07 study). On the whole, serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin in combination with an infusional 5-FU/LV de Gramont schedule (FOLFOX4 regimen) than infusional 5-FU/LV alone (de Gramont regimen) and oxaliplatin in combination with a bolus 5-FU/LV Roswell Park schedule (FLOX regimen) than bolus 5-FU/LV alone (Roswell Park regimen).

Evidence from the X-ACT study demonstrated that capecitabine therapy was at least equivalent in disease-free survival to the bolus Mayo Clinic 5-FU/LV regimen for patients with resected Stage III colon cancer. In terms of relapse-free survival, capecitabine monotherapy was significantly better than bolus 5-FU/LV. The safety and tolerability profile of capecitabine was superior to that of the Mayo Clinic 5-FU/LV regimen, but has not been evaluated in comparison with the less toxic 5-FU/LV regimens currently in common use in the UK.

Cost-effectiveness

Based on the assumptions regarding long-term survival, the results of the independent health economic assessment suggest that both capecitabine and FOLFOX4 appear to have favourable cost-effectiveness profiles in comparison with 5-FU/LV regimens (Mayo and de Gramont schedules), based on levels of cost-effectiveness which are currently considered by NHS policymakers to represent acceptable value for money. Indirect comparisons suggest that FOLFOX4 is cost-effective compared with the Mayo Clinic 5-FU/LV regimen, although it may not be deemed cost-effective by policymakers in comparison with capecitabine. These economic comparisons could only be assessed fully following a trial that directly compared these two regimens.

The mean age of patients in both the MOSAIC and X-ACT studies is considerably lower than that observed in clinical practice and, as a result, the cost-effectiveness analyses may overestimate long-term overall survival for patients in all treatment arms, owing to the shorter life expectancy of these more elderly patients. The marginal benefits of capecitabine and FOLFOX4 versus their respective 5-FU/LV comparators may therefore be overestimates and, as a result, the estimated marginal costs-effectiveness ratios may have been underestimated.

Recommendations for further research

The following areas are suggested for further research.

- A comparison of the effectiveness, tolerability, patient acceptability and costs of different oxaliplatin/fluoropyrimidine schedules in the adjuvant setting.
- Large trials to determine the effects of treatment duration on efficacy.
- Consideration of the best approach to ensure compliance and monitoring of adverse events.
- Future cancer trial protocols incorporating more detailed resource data collection strategies and reporting of summary statistics that are of use within economic evaluations.
- Identification of those subgroups of patients who benefit the most from chemotherapy.
- Methods for estimating mean survival, both in non-curative interventions (in which the survival time is prohibitively long and thus prevents estimation of mean survival) and in curative treatments.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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