Rapid review

A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

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Treatment of advanced colorectal cancer

Executive summary

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Executive summary

Background

Description of proposed service

The service evaluated in this review is the use of irinotecan, oxaliplatin and raltitrexed, as both monotherapy and combination therapy, in the first- and second-line treatment of patients with advanced colorectal cancer.

Epidemiology

Colorectal (large bowel) cancer is the second most common cancer in the UK after lung cancer. In 1992, a total of 29,664 new cases were registered in England and Wales, an incidence of 56.6 per 100,000 population. Colorectal cancer is also the second most common cause of cancer death in the UK, causing almost 15,000 deaths in England and Wales in 1998. It affects men and women almost equally. Incidence rises sharply with age but is fairly evenly distributed across the social classes, and within the UK there is little age-specific geographic variation.

Advanced colorectal cancer has been defined as colorectal cancer that, at presentation or recurrence, is either metastatic or so locally advanced that surgical resection is unlikely to be carried out with curative intent. Around 29% of patients who present with colorectal cancer have distant metastases at the time of presentation. About 80% of patients diagnosed with colorectal cancer undergo surgery. Many have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), but over 50% of patients who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastasis (typically presenting within 2 years of initial diagnosis). Median survival from diagnosis of metastatic disease is 6–9 months, and during this time patients may develop a wide range of physical and psychological symptoms, which detract from their quality of life and often require hospital admission.

Colorectal cancer is rare below 40 years of age, and 41% of patients are over the age of 75 years. Although 52% of deaths from colorectal cancer occur in the over-75 age group, colorectal cancer is nonetheless a significant cause of premature death as well as of morbidity. The aim of treatment in patients with advanced disease is to improve both the duration and quality of the patient's remaining life.

Objectives

The objectives of this review are:

1. to evaluate the relative clinical effectiveness of irinotecan, oxaliplatin and raltitrexed in terms of disease progression rates
2. to estimate their relative effect on overall survival and quality-of-life-adjusted survival
3. to evaluate their side-effect profiles
4. to estimate the incremental cost-effectiveness of the three drugs in comparison with conventional therapy
5. to estimate the overall cost associated with the use of these drugs in England and Wales.

Methods

A systematic review of the literature, involving a range of databases, was conducted. Full details are described in the main report.

Results

Number and quality of studies, and direction of evidence

Irinotecan

Six randomised controlled trials relating to the use of irinotecan as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Only preliminary data were available for four of these, of which three had been published only in abstract form. The two completed studies found that the combination of irinotecan with fluorouracil and folinic acid (FU/FA) was associated with significantly longer median overall and progression-free survival than FU/FA alone. Irinotecan alone appeared comparable with FU/FA alone. However, irinotecan plus FU/FA was associated with a higher level of toxicity than FU/FA alone.

Seven studies relating to the use of irinotecan as second-line treatment of advanced colorectal

cancer were judged to have met the inclusion criteria. Full reports were available for only two of these; for the remainder, only preliminary data were available in abstract form. One of the two completed studies compared irinotecan with best supportive care (BSC), and the other compared it with FU/FA. Irinotecan was found to significantly increase median overall survival compared with FU/FA, although it did not increase median progression-free survival significantly. Irinotecan was associated with increased overall survival compared with BSC, but it is not clear to what extent this should be attributed specifically to irinotecan and to what extent to other factors. Irinotecan significantly increased pain-free survival and time to deterioration of performance status in comparison with BSC, but not in comparison with FU/FA. There is also some preliminary evidence that combination second-line irinotecan/FU/FA therapy may increase progression-free survival compared with FU/FA alone. As second-line treatment, irinotecan was again associated with a higher level of toxicity than FU/FA.

Oxaliplatin

Seven studies relating to the use of oxaliplatin as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Of these, two studies compared only chronomodulated versus fixed-rate oxaliplatin plus FU/FA. Full reports were available for only two of the remaining studies; for the remainder, only preliminary data were available in abstract form. Oxaliplatin plus FU/FA was found to increase median progression-free survival compared with FU/FA alone. In both studies for which final results were available, so many patients received chemotherapy subsequent to the study medication that the impact of oxaliplatin on overall survival has been obscured. Oxaliplatin appeared to be associated with increased toxicity compared with FU/FA regimens.

Three studies relating to the use of oxaliplatin as second-line, or first- and second-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Only preliminary results have been published, in abstract form, in relation to these studies. These preliminary results suggest that median progression-free survival may be longer in patients receiving oxaliplatin plus 5FU than in those receiving either 5FU or irinotecan monotherapy.

Raltitrexed

Four studies relating to the use of raltitrexed as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Full reports were available for only two of these studies. When the results were statistically significant, raltitrexed was associated with shorter progression-free and overall survival than FU/FA. Although raltitrexed was associated with less toxicity than the Mayo bolus FU/FA regimen, it was associated with more deaths that were considered to be possibly treatment related.

Summary of benefits

There is good evidence to suggest that the use of a combination of irinotecan and FU/FA in the first-line treatment of advanced colorectal cancer can extend both median progression-free and overall survival by 2–3 months compared with either FU/FA alone or irinotecan alone, although at the cost of increased toxicity compared with FU/FA alone. As second-line treatment, irinotecan monotherapy appears to extend median progression-free survival by approximately 1 month and overall survival by approximately 2 months compared with FU/FA alone, again at the cost of increased toxicity. There is also some preliminary evidence to suggest that combination irinotecan/FU/FA therapy after FU/FA failure may extend median progression-free survival by approximately 2 months and overall survival by almost 3 months compared with FU/FA alone.

There is also good evidence to suggest that, when used as first-line therapy, the combination of oxaliplatin with an infusional FU/FA regimen extends median progression-free survival by 2–3 months compared with FU/FA alone, although again with increased toxicity. This combination may also prolong overall survival, although this is not clear because of the extensive use of second-line oxaliplatin in patients randomised to FU/FA alone, which would dilute the evidence of the efficacy of oxaliplatin in the oxaliplatin arm. In addition, the improved response rate achieved by the addition of oxaliplatin to FU/FA may enable larger numbers of patients to undergo potentially curative surgical resection of liver metastases. Preliminary data suggest that, as second-line treatment, oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan monotherapy.

In comparison with FU/FA, raltitrexed used as first-line therapy appears to reduce both progression-free and overall survival, and is associated with a higher mortality rate. Thus, there seems no advantage in using raltitrexed to treat advanced colorectal cancer in patients who ▶

can tolerate FU/FA treatment, and further research is required to determine whether it has a role in the treatment of the patient group for whom it is licensed, namely those few patients with specific metabolic intolerance to 5FU who would not be too frail for 5FU treatment. This is a smaller patient group than AstraZeneca, in their submission to the National Institute for Clinical Excellence, suggest would benefit from raltitrexed.

Costs

The cost of treatment with 5FU and FA by the de Gramont infusional regimen is estimated to be £2500 per month when given on an inpatient basis or £1500 when given on an outpatient basis. The addition of oxaliplatin adds £800 per month to this regimen, and addition of irinotecan adds £1000. The Mayo 5FU regimen is less costly at £1100 per month. The cost of treatment with raltitrexed has been shown by one economic study[1] to be similar to that for the Mayo regimen (£781 for raltitrexed, £834 for Mayo), although these published costs of Mayo treatment are lower than the estimate calculated by the authors of this review. The estimated cost of second-line treatment with irinotecan as a single agent is £1800.

The estimation of the total costs per patient for any treatment is dependent on the mean treatment duration. For first-line treatment with irinotecan, this mean value is not known, so there is great uncertainty in the calculation of treatment costs.

Furthermore, in practice, treatments may be given to patients for limited periods. The estimates of additional treatment costs compared with 5FU are based on mean treatment times from the trials, except for first-line irinotecan.

Total treatment costs for oxaliplatin are £5330 greater than costs for inpatient treatment with the de Gramont FU/FA regimen. The same comparison for irinotecan shows an additional cost of £11,400. It should be noted that there is more uncertainty in the estimate for irinotecan than for oxaliplatin. The differences with the Mayo regimen are greater. The total cost of single-agent irinotecan for second-line treatment is less than that of 5FU by the de Gramont regimen. A bolus regimen (such as Mayo) is not normally appropriate for second-line treatment. However, not all patients who may be eligible for second-line treatment with irinotecan (approximately 65%) would currently receive 5FU. For these patients, the relevant comparison is with BSC. Assuming that BSC costs are the same for all patients (i.e. patients treated with irinotecan eventually incur the same BSC costs as patients having no second-line treatment), the additional cost of giving patients irinotecan is £7600.

Cost-effectiveness

The calculations of cost-effectiveness are based on progression-free survival, rather than survival, because when chemotherapy is given subsequent to the allocated first-line regimens, survival cannot be uniquely related to the allocated therapy. The use of progression-free survival in place of survival has considerable implications on the results of the economic analysis. Oxaliplatin shows greater improvement than irinotecan in progression-free survival, compared with 5FU, based on our analysis of the progression-free survival curves; however, no survival benefit has been shown in clinical trials with oxaliplatin, whereas it has with irinotecan. For second-line treatment (after which smaller proportions of patients had further chemotherapy compared with after first-line therapy), cost-effectiveness ratios were estimated on the basis of both progression-free survival and survival. The results of the two estimates are different.

The marginal cost per progression-free year for oxaliplatin compared with the de Gramont 5FU regimen is £23,000. The equivalent cost for irinotecan is £58,400. These figures are obviously dependent on the cost estimates that, as previously noted, are more uncertain for irinotecan than for oxaliplatin. Second-line treatment with irinotecan (single-agent therapy) is less expensive than the inpatient de Gramont regimen. If it is assumed that all treatments are given on an outpatient basis, the marginal cost per progression-free year is unchanged for oxaliplatin, £49,000 for irinotecan and £26,400 for second-line irinotecan.

For second-line treatment, the marginal cost per life-year gained (i.e. based on survival benefit) is zero when irinotecan is compared to inpatient treatment with the de Gramont regimen, £11,180 when compared to outpatient de Gramont, and between £17,700 and £28,200 when compared to BSC.

1. Kerr D, O'Connor KM. An economic comparison of the net clinical benefit and treatment costs of raltitrexed and 5-fluorouracil + leucovorin (Mayo regimen) in advanced colorectal cancer. *Journal of Medical Economics* 1999;**2**:123–32.

An illustrative analysis was undertaken to estimate the effect of taking quality of life into account. The assumptions are considered to be too uncertain to base conclusions on the results.

Because there is no benefit in either progression-free survival or survival when treatment with raltitrexed is compared with 5FU, a cost-effectiveness analysis is not appropriate.

Conclusions

When used as first-line therapy, the combination of either irinotecan or oxaliplatin with an infusional FU/FA regimen appears to extend median progression-free survival by 2–3 months compared with FU/FA alone, although with increased toxicity; irinotecan has also been shown to extend overall survival. However, raltitrexed appears to reduce both progression-free and overall survival compared with FU/FA. When used as second-line treatment, irinotecan monotherapy appears to extend median progression-free survival by approximately 1 month and overall survival by approximately 2 months compared with FU/FA alone, again at the cost of increased toxicity. Preliminary data suggest that, as second-line treatment, oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan monotherapy.

Recommendations for research

Evidence is needed of the relative merits of irinotecan and oxaliplatin for patients with advanced colorectal cancer, the best time to introduce these drugs (as first- or second-line therapy), and whether both should routinely be offered to a single patient and, if so, in what order.

Randomised controlled trials are also required to explore:

- the relative efficacy of second-line 5FU plus mitomycin C versus irinotecan or oxaliplatin
- whether raltitrexed is beneficial compared with either BSC alone or other agents in patients with specific metabolic intolerance of 5FU
- the relative efficacy of different sequences of therapies
- the optimum duration of therapy (i.e. whether it should be continued to disease progression, death or unacceptable toxicity, or only until response, with or without consolidation)
- the relative efficacy of oxaliplatin and 5FU in patients with a family history of colorectal cancer caused by the *HNPCC* gene mutation.

Given the palliative objectives of therapy, research is required to address the issue of measuring quality of life in patients with terminal cancer.

Publication

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NHS R&D HTA Programme

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

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