

Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation

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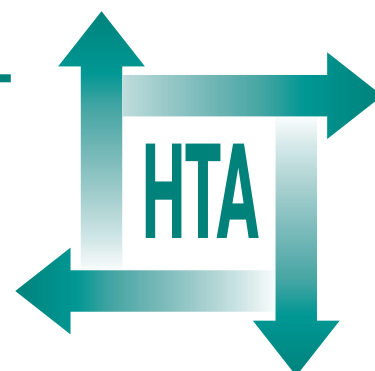
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Executive summary

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Executive summary

Description of proposed service

The service evaluated in this review is the use of capecitabine and tegafur with uracil (UFT/LV) as first-line treatments for patient with metastatic colorectal cancer.

Epidemiology

Colorectal cancer (cancers of the colon and rectum combined) accounts for 13% of all cancers in England and Wales and is the second most common cancer in the UK, after lung cancer. In 1997, 28,900 cases of colorectal cancer were diagnosed in England and Wales, of which about two-thirds were in the colon and one-third in the rectum. Incidence increases with age. The median age of patients at diagnosis is just under 70 years.

Approximately 80% of patients with colorectal cancer undergo surgery and, of these, 40% will remain disease-free in the long term.

Approximately 20% of patients with colorectal cancer present with advanced disease and, of these, approximately 50% will have liver metastases. Median survival after diagnosis of metastatic disease is approximately 6–9 months. Patients may have a variety of symptoms, both physical and psychological, which detract from their quality of life and often require hospital admission.

Colorectal cancer is a significant cause of premature mortality, with 48% of deaths occurring in the under-75 age group. It is also a significant cause of morbidity. The main aims of treatment for patients with metastatic colorectal cancer are to relieve symptoms, increase survival and improve quality of life.

Number and quality of studies and direction of evidence

Two published randomised controlled trials (RCTs) of capecitabine, along with one separate report pooling data from the same two studies, met the inclusion criteria. These studies compared treatment with capecitabine to treatment with the

Mayo clinic 5-fluorouracil/leucovorin (5-FU/LV) regimen. Duration of response, time to disease progression or death, time to treatment failure and overall survival were found not to be significantly different between the two treatments. Overall response rates, assessed by the investigator, were significantly greater in both trials in the capecitabine group, whereas overall response rates, as assessed by an independent review committee, were found to be significantly greater for the capecitabine group in one of the trials and pooled data. With regard to toxicity, patients in the capecitabine group reported less diarrhoea, stomatitis, nausea and alopecia of all grades than those in the 5-FU/LV groups. Those in the capecitabine group also had significantly less grade 3–4 neutropenia and less frequent hospitalisation for adverse events. Hand–foot syndrome and grade 3 hyperbilirubinaemia was significantly greater in the capecitabine group. Despite this improved toxicity profile, the reported health-related quality of life did not differ significantly between the capecitabine and 5-FU/LV groups in either trial.

Two RCTs of treatment with Uftoral[®]/leucovorin (UFT/LV) met the inclusion criteria. One trial compared UFT/LV with the standard Mayo 5-FU/LV regimen and the other compared UFT/LV with a modification of the Mayo regimen. There were no significant differences with regard to overall response rates, duration of response or survival between UFT/LV and 5-FU/LV in either trial. Time to disease progression was significantly inferior for the UFT/LV group than the 5-FU/LV group in one study, although there was no difference in time to disease progression between UFT/LV and 5-FU/LV in the second study. Treatment with UFT/LV was associated with significantly less diarrhoea, nausea/vomiting, mucositis, neutropenia and thrombocytopenia of all grades compared with 5-FU/LV in one study and fewer episodes of stomatitis/mucositis, neutropenia, thrombocytopenia and anaemia of any grade in the other study. With regard to grade 3–4 toxicity, mucositis, neutropenia, thrombocytopenia and anaemia were much less frequent in the UFT/LV group in one study and grade 3–4 stomatitis/mucositis and neutropenia were much less common in the second study. ►

Significantly increased bilirubin was more common among UFT/LV patients than in those treated with 5-FU/LV in the first study. As with the capecitabine studies, despite this improved toxicity profile, reported health-related quality of life did not differ significantly between the UFT/LV and 5-FU/LV groups in either trial.

Economic evidence reviewed in this analysis includes a pharmacoeconomic study of UFT costs in South America and two resource-use studies, one relating to evidence from the Hoff capecitabine trial and the other to results from the UFT/LV trial by Carmichael. None of the evidence identified was directly applicable to the situation of England and Wales. Two sponsor submissions received by the National Institute for Clinical Excellence (NICE) from Roche and Bristol-Myers Squibb were also reviewed.

Summary of benefits

There is good evidence to suggest that treatment with capecitabine improves overall response rates and has an improved adverse effect profile in comparison with 5-FU/LV treatment with the Mayo regimen, with the exception of hand-foot syndrome. There is no evidence comparing capecitabine with infusional 5-FU schedules such as the de Gramont or modified de Gramont regimens, both commonly used as standard treatment in the UK.

Time to disease progression or death after treatment with UFT/LV in one study appears to be shorter than after treatment with 5-FU/LV with the Mayo regimen. There is no evidence comparing UFT/LV with treatment with the de Gramont or modified de Gramont regimen. Treatment with UFT/LV had an improved adverse effect profile compared with 5-FU/LV treatment with the Mayo regimen.

Neither capecitabine nor UFT/LV appeared to improve health-related quality of life. Information on patient preference was available for UFT/LV only from a small crossover trial. Patients appeared strongly to prefer treatment with UFT/LV over 5-FU/LV.

Costs

Costs were estimated through resource-use data taken from the published trials and the unpublished sponsor submissions. Unit costs were

taken from published sources, where available. The total cost of capecitabine and UFT/LV treatments were estimated at £2111 and £3375 respectively, compared with the total treatment cost for the Mayo regimen of £3579. Cost estimates were also presented for the modified de Gramont and inpatient de Gramont regimens. These were £3684 and £6155, respectively.

Cost-effectiveness

An economic evaluation was undertaken to compare the cost-effectiveness of capecitabine and UFT/LV with three intravenous 5-FU/LV regimens widely used in the UK: the Mayo, the modified de Gramont regimen and the inpatient de Gramont regimens.

No survival advantage was shown in the RCTs of the oral drugs against the Mayo regimen. Cost minimisation analyses were therefore undertaken for both oral therapies against the Mayo regimen. Cost savings of capecitabine and UFT/LV over the Mayo regimen were estimated to be £1461 and £209, respectively. Drug acquisition costs were higher for the oral therapies than for the Mayo regimen, but were offset by lower administration costs. Adverse event treatment costs were similar across the three regimens.

No direct evidence comparing either capecitabine or UFT/LV treatment with de Gramont regimens was identified and therefore an indirect comparison was undertaken for the purposes of economic evaluation. On the basis that no proven survival difference between the Mayo and the de Gramont regimens was identified, it was inferred that there was no survival difference between the oral drugs and the de Gramont regimens. Cost minimisation analyses of the oral therapies against the de Gramont regimens were performed. Cost savings of capecitabine and UFT/LV over the modified de Gramont regimen were estimated to be £1353 and £101, respectively. Cost savings of capecitabine and UFT/LV over the inpatient de Gramont regimen were estimated to be £4123 and £2870, respectively.

Cost-effectiveness analyses were also undertaken, for illustrative purposes, to explore the impact of adopting an assumption of survival benefit of de Gramont regimens over the oral regimens. Infusional regimens have been shown to be more effective than bolus regimens in terms of progression-free survival, tumour response

and toxicity. The impact of a potential difference in progression-free survival between the oral drugs and the infusional regimens was explored in terms of the impact on the cost per progression-free life year gained. The results are illustrative only. Further direct evidence on the survival benefits and costs of oral therapies relative to infusional regimens is required before any robust conclusions can be drawn from this type of analysis.

Conclusion

The results show that there are cost savings associated with the use of oral therapies. No survival difference has been proven between the oral drugs and the Mayo regimen. In addition, no evidence of a survival difference between the Mayo regimen and the de Gramont regimens has been identified. However, improved progression-free survival and an improved adverse event profile have been shown for the de Gramont regimen over the Mayo regimen and these need to be taken into consideration. These issues can only be indirectly addressed in the absence of direct randomised comparisons between the oral drugs and optimum infusional 5-FU regimens.

Need for further research

The following points have been identified as areas requiring further research:

- Quality of life data should be included in trials of colorectal cancer treatments. Well-validated instruments should be used and this research should be conducted by independent researchers. It may be necessary to use more than one instrument in order to identify differences in quality of life and then the components of quality of life that vary with different treatments.

- More research is needed to determine the place of effective oral treatments in the treatment of colorectal cancer. This should focus on when such treatments should be given alone and when they should be given in combination with other chemotherapeutic agents. Research is needed on the combination of oral agents with other chemotherapy agents (notably irinotecan and oxaliplatin) and novel agents.
- Some types of patients may benefit more from oral treatment than others. Research is needed to determine what safety mechanisms are needed in order to ensure compliance and the monitoring of adverse effects.
- The optimum duration of treatment needs to be determined with respect to, for example, disease progression, response, unacceptable toxicity or death. Intermittent treatment with a pause after 12 weeks for those with stable or responding disease also needs to be considered.
- The issue of patient preference must be given careful consideration in future trials and all trials should incorporate the measurement of patient preference.
- In order to make a precise estimate of the cost-effectiveness of capecitabine and UFT/LV versus modified de Gramont treatment, a phase III comparative trial would be necessary to determine whether there was any survival advantage and to collate the necessary economic data. This would also give clinicians clear information on survival to present to patients who can then make an informed choice with regard to treatment.

Publication

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