Cost-effectiveness of combination chemotherapy (oxaliplatin or irinotecan in combination with 5-FU/FA) compared with 5-FU/FA alone

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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 use of a combination therapy of either oxaliplatin or irinotecan with 5-fluorouracil (5-FU) and folinic acid (FA) for the treatment of colorectal cancer.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with advanced colorectal cancer.

Setting
The setting appears to have been a hospital. The authors did not state where the economic study was carried out, although it may have been in the UK.

Dates to which data relate
The effectiveness and resource utilisation data were collected from two studies published in 2000. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Outcomes assessed in the review
The outcomes assessed in the review were progression-free survival for the irinotecan plus 5-FU/FA and 5-FU/FA alone therapies, and time to disease progression for the oxaliplatin plus 5-FU/FA and 5-FU/FA alone therapies. Both progression-free survival and time to disease progression were considered equivalent outcomes measures. The response rate for the therapies under study, and the number (and percentage) of patients experiencing grade 3/4 toxicities (both haematological and haematological toxicities) were also reported.

Study designs and other criteria for inclusion in the review
The two studies included in the review were Phase III trials. At least one of them was a multicentre randomised trial. The authors justified their inclusion because they formed the basis of the licence applications for the two agents, oxaliplatin and irinotecan.
Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported. The use of the extracted data was justified on the grounds that there were no studies comparing the two combined therapies under study, irinotecan plus 5-FU/FA and oxaliplatin plus 5-FU/FA.

Number of primary studies included
Two studies were included in the review (de Gramont et al. and Douillard et al., see Other Publications of Related Interest).

Methods of combining primary studies
A narrative method was used to include the results of the primary studies. The authors reported that the effectiveness data for oxaliplatin plus 5-FU/FA versus 5-FU/FA alone were obtained from the de Gramont et al. study. The effectiveness data for irinotecan plus 5-FU/FA versus 5-FU/FA alone were obtained from the Douillard et al. study.

Investigation of differences between primary studies
Not reported.

Results of the review
Progression-free survival was significantly longer for oxaliplatin plus 5-FU/FA (9 months, 95% confidence interval, CI: 8.04 - 9.63) than for 5-FU/FA alone (6.2 months, 95% CI: 5.45 - 7.39), (p=0.001). Also, for irinotecan plus 5-FU/FA (6.7 months) compared with 5-FU/FA alone (4.4 months), (p<0.001).

The response rate was significantly higher for oxaliplatin plus 5-FU/FA (49.5%, 95% CI: 46.1 - 53.0) than for 5-FU/FA alone (28.6%, 95% CI: 25.5 - 31.7), (p=0.001). Also, for irinotecan plus 5-FU/FA (34.8%, 95% CI: 28.2 - 41.9) versus 5-FU/FA alone (21.9%, 95% CI: 16.2 - 28.5), (p=0.005).

The percentage of patients experiencing haematological and non-haematological toxicities appeared to be higher for the combination therapies than for 5-FU/FA alone.

The numbers of patients experiencing haematological toxicities were:

in the oxaliplatin plus 5-FU/FA group (209 patients), 2 (0.9%) for infection with grade 3/4 neutropenia, 87 (41.7%) neutropenia, 5 (2.5%) thrombocytopenia, and 7 (3.3%) anaemia;

in the 5-FU/FA group (208 patients; de Gramont et al. study), none (0%) for infection with grade 3/4 neutropenia, 11 (5.3%) neutropenia, 1 (0.5%) thrombocytopenia, and 5 (2.5%) anaemia;

in the irinotecan plus 5-FU/FA group (199 patients), 4 (2.0%) for infection with grade 3/4 neutropenia, 10 (5.0%) fever without infection with grade 3/4 neutropenia, 81 (40.7%) neutropenia, 36 (18.1%) leucopenia, and 6 (3.0%) anaemia;

in the 5-FU/FA group (186 patients; Douillard et al. study), none (0%) for infection with grade 3/4 neutropenia, 2 (1.1%) fever without infection with grade 3/4 neutropenia, 20 (10.8%) neutropenia, 6 (3.2%) leucopenia, and 3 (1.6) anaemia.
The number of patients experiencing non-haematological toxicities (diarrhoea, nausea, vomiting and mucositis) among other toxicities reported (asthenia, anorexia, abdominal pain, pain, cholinergic syndrome, hand and foot syndrome, cutaneous signs, weight loss and infection) were:

in the oxaliplatin plus 5-FU/FA group (209 patients), 25 (11.9%) diarrhoea, 12 (5.7%) nausea, 12 (5.8%), vomiting, and 12 (5.8%) mucositis;

in the 5-FU/FA group (208 patients; de Gramont et al. study), 11 (5.3%) diarrhoea, 4 (2.0%) nausea, 4 (2.0%) vomiting, and 3 (1.5%) mucositis;

in the irinotecan plus 5-FU/FA group (199 patients), 43 (21.6%) diarrhoea, 7 (3.5%) nausea, 10 (5.0%) vomiting, 6 (3.0%) mucositis;

in the 5-FU/FA group (186 patients; Douillard et al. study), 19 (10.2%) diarrhoea, 4 (2.2%) nausea, 3 (1.6%) vomiting, and 4 (2.2%) mucositis.

Measure of benefits used in the economic analysis
The summary measures of benefit used in the economic analysis were progression-free survival and response rates, as reported in the 'Results of the Review' section. The authors also reported the number of patients that needed to be treated per additional responder treated with the combination therapies, in comparison with 5-FU/FA alone.

Direct costs
Although the authors reported that the NHS perspective was adopted, the only direct costs included were the drug acquisition costs. The authors stated that the administration costs of the alternative therapies considered at analysis were the same, and were therefore not included. The resource quantities (related to the doses of the drugs and the number of cycles administered) were reported separately from the costs. The resource utilisation data were obtained from the studies included in the review. The drug unit costs were taken from Monthly Index of Medical Specialities (MIMS) and British National Formulary (BNF). Therefore, the costs were estimated from published data. As there were two regimens for the irinotecan plus 5-FU/FA group and its corresponding 5-FU/FA group, the authors estimated a weighted cost per patient by considering both regimens. Discounting was not performed because the time period considered at analysis was less than 2 years. The study reported the average costs. The price year was not given.

Statistical analysis of costs
Not reported.

Indirect Costs
No indirect costs were reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
Sensitivity analyses were performed on both the outcomes and costs to investigate variability in the data. The variables investigated were progression-free survival (+/- 2.5%), response rates (according to their 95% confidence interval, CI) and the cost data (+/- 10%). The number of patients needed to be treated per additional responder was also considered in the sensitivity analyses. All the sensitivity analyses compared the lower CI limit or estimate for the corresponding 5-FU/FA group (and vice versa). Therefore, 2-way sensitivity analyses appear to have been performed.
Estimated benefits used in the economic analysis
Incremental progression-free survival was 2.8 months for patients treated with oxaliplatin plus 5-FU/FA when compared to 5-FU/FA alone. The corresponding value for patients treated with irinotecan plus 5-FU/FA, compared to 5-FU/FA alone, was 2.3 months.

The number of patients needed to be treated per additional responder was 5 under the oxaliplatin plus 5-FU/FA therapy when compared to 5-FU/FA alone. The corresponding number for patients treated under the irinotecan plus 5-FU/FA therapy, compared to 5-FU/FA alone, was 8.

The benefits appear to have been estimated over a 1-year period, although it was not reported. However, although relevant, side effects were not considered in the economic analysis.

Cost results
The average cost per patient was 9,216 for oxaliplatin plus 5-FU/FA patients, and 3,003 for the corresponding 5-FU/FA patients, and 9,117 for irinotecan plus 5-FU/FA patients, and 1,889 for the corresponding 5-FU/FA patients.

The authors reported that they did not include the costs of the side effects, because there was insufficient information in the reviewed studies on the nature and duration of treatment for the toxicities.

Synthesis of costs and benefits
The estimated benefits and costs were combined using incremental cost-effectiveness ratios (ICERs).

The incremental cost per additional progression-free year was 26,665 (range: 21,421 - 31,909) for oxaliplatin plus 5-FU/FA when compared to 5-FU/FA alone, and 30,171 (range: 23,691 - 36,651) for irinotecan plus 5-FU/FA when compared to 5-FU/FA alone.

The incremental cost per additional percentage response rate obtained was 297 with oxaliplatin plus 5-FU/FA when compared to 5-FU/FA alone, and 449 with irinotecan plus 5-FU/FA when compared to 5-FU/FA alone.

When the number of patients needed to be treated per additional responder was considered as the summary measure of benefit, the ICER obtained was 31,065 per year per additional responder for patients receiving oxaliplatin plus 5-FU/FA, compared to patients receiving 5-FU/FA alone. The ICER was 46,343 per year per additional responder for patients receiving irinotecan plus 5-FU/FA, compared to patients receiving 5-FU/FA alone.

Authors' conclusions
Both combinations offered comparable benefits in terms of the effectiveness and incremental cost-effectiveness ratios (ICERs), over the 5-fluorouracil/folinic acid (5-FU/FA) therapy alone, for the treatment of advanced colorectal cancer.

CRediT COMMENTARY - Selection of comparators
The comparator used seems to have been chosen because it represented current practice in the authors' setting. You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. Only two studies were included in the review and it is not clear if these have been chosen selectively. The effectiveness estimates were combined using narrative methods. The authors did not consider the impact of differences between the primary studies on the effectiveness estimates derived. They also reported that the overall survival was not considered as an outcome in the review, because the results from the primary studies could not be accurately attributed to the treatments.
Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analyses. The authors justified the choice of progression-free time and overall response rate because these were the main health outcomes assessed in the primary studies included in the review.

Validity of estimate of costs
The authors reported that the NHS perspective was adopted. However, the only costs finally considered were the drug acquisition costs. The authors justified the exclusion of the drug administration costs because they were the same, independently of the administered therapy. However, they stated that the total costs of the treatments were not calculated, as there were insufficient data available. The costs derived from the side effects were not included in the study, although they were relevant. Their exclusion may have led to an underestimation of the costs of the oxaliplatin plus 5-FU/FA and irinotecan plus 5-FU/FA therapies, due to the fact that these therapies generated more toxicity among the patients receiving them than 5-FU/FA alone. These points may have limited the reliability of the results obtained. The drug resource quantities were reported separately from the costs, but the price year was not given. Thus, any reflation exercise to other settings will be hindered.

Other issues
The authors mentioned other studies that used the same primary studies but reported different health outcomes (e.g. overall survival), other than this no comparisons were made. The issue of the generalisability of the results to other settings was not addressed. The authors’ conclusions reflected the scope of the analyses.

Implications of the study
The study shows that the ICERs for oxaliplatin plus 5-FU/FA and irinotecan plus 5-FU/FA, compared to 5-FU/FA alone, are in line with other treatments that have been accepted by the Health Technology Assessment of the UK National Institute of Clinical Excellence (e.g. paclitaxel for the treatment of ovarian cancer). Oxaliplatin plus 5-FU/FA was more cost-effective than irinotecan plus 5-FU/FA. However, not all of the relevant costs related to these therapies were included in the analysis. Therefore, the inclusion of these costs could change the conclusions drawn in the other study.

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Economic evaluation funded by Sanofi-Synthelabo.

Bibliographic details

Other publications of related interest


**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antineoplastic Combined Chemotherapy Protocols /adverse effects /therapeutic use /economics; Camptothecin /analogs & derivatives /therapeutic use /economics; Colorectal Neoplasms /drug therapy; Cost-Benefit Analysis; Drug Administration Schedule; Fluorouracil /administration & dosage /adverse effects /economics; Humans; Leucovorin /adverse effects /economics; Organoplatinum Compounds /administration & dosage /economics /adverse effects; Quinazolines /administration & dosage /adverse effects

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