Two schedules of second-line irinotecan for metastatic colon carcinoma: economic evaluation of a randomized trial

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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
Two schedules of second-line irinotecan for patients with metastatic colon carcinoma were examined. The schedules were weekly irinotecan (125 mg/m2 once a week for 4 weeks, followed by a 2-week break) versus irinotecan once every 3 weeks (350 mg/m2 or 300 mg/m2).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with metastatic colorectal cancer refractory to 5-FU.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The dates when the effectiveness and resource use data were collected were not reported. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The study was powered to detect a 15% difference in one-year survival between the groups. The method of sample selection was not reported as the methods and details of the study had been published already. Overall, 291 patients were included in the study, 95 in the weekly irinotecan group and 196 in the irinotecan every 3 weeks group. The patients in the weekly irinotecan group had a mean age of 63 years and 62% were women. The patients in the irinotecan every 3 weeks group had a mean age of 62.7 years and 58% were women.

Study design
This was a prospective, Phase III, open-label, randomised, multi-centre clinical trial. The length of follow-up could have been one year. Further details of the study design were not provided.

**Analysis of effectiveness**

Several outcome measures were used in the analysis:

- the one-year survival rate,
- median survival,
- the median time to disease progression,
- efficacy,
- Grade 3-4 diarrhoea,
- Grade 3-4 neutropenia, and
- treatment-related mortality.

The utility values were also estimated but were not reported. The study groups were comparable at baseline in terms of demographics and prognostic features.

**Effectiveness results**

The one-year survival rate was 46% in the weekly group and 41% in the once every 3 weeks group, (p=0.42).

The median survival rate was 9.9 months in both groups, (p=0.43).

The median time to disease progression was 4 months in the weekly group and 3 months in the once every 3 weeks group, (p=0.54). Similar efficacy was observed.

The frequency of Grade 3-4 diarrhoea was 36% in the weekly group and 19% in the once every 3 weeks group, (p=0.002).

The frequency of Grade 3-4 neutropenia was 29% in the weekly group and 34% in the once every 3 weeks group, (p=0.35).

The rate of treatment-related mortality was 5.3% in the weekly group and 1.6% in the once every 3 weeks group, (p=0.12).

**Clinical conclusions**

The effectiveness analysis showed that irinotecan administered once every 3 weeks led to fewer patients experiencing Grade 3-4 diarrhoea. The other outcomes were comparable between the groups.

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated by combining utility values and survival data, both derived from the clinical trial. The utility values were estimated using the European Organization for Research and Treatment of Cancer QOL instrument (QLQ-C30). Missing values were imputed by carrying forward the last known value. Survival was considered equivalent in both arms of the trial. Discounting was not applied because of the short time horizon.
Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe. The unit costs were presented separately from the quantities of resources used for few cost items. The health services included in the economic evaluation were chemotherapy treatment administration (e.g. physician, nurse, pharmacy, supplies and hotel), disease-related imaging studies and blood work, supportive treatment-related medications (e.g. anti-emetics), hospitalisation, non-treatment-related medications and non-treatment-related tests. The cost/resource boundary of the health service payer was adopted. Resource use was estimated using a sample of patients included in the clinical trial. The costs were derived using the bills from a sub-set of patients on the trial and from Medicare reimbursement rates. Specific cost-to-charge ratios were applied to derive appropriate cost estimates. The costs were inflated to 2001 prices using the medical care component of the Consumer Price Index.

Statistical analysis of costs
A multiple regression analysis was carried out to explore the relationship between baseline patient characteristics and treatment costs, using costs that were log-transformed to account for their skewed distribution.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars (§).

Sensitivity analysis
Two-way and multivariate sensitivity analyses were performed to examine the robustness of the cost-utility ratios to variations in several parameters. The parameters investigated were chemotherapy cost, utilities, hospitalisation costs, chemotherapy administration, monitoring, and ancillary treatments and tests. The impact of changing chemotherapy dosages was also investigated. A bootstrap analysis was used to recalculate the cost-utility ratio on 1,000 random sub-samples with replacement.

Estimated benefits used in the economic analysis
The difference in QALYs between the two treatments was 6.3 in favour of the once every 3 weeks schedule.

In the bootstrap analysis, the average difference in QALYs was 6.4 (95% confidence interval: 5.8 - 7.1 days).

Cost results
The difference in costs between the two treatments was $1,362 in favour of the weekly schedule.

The regression analysis showed that only treatment, body surface area and duration of therapy predicted the treatment costs. The chemotherapy costs and its administration were the main cost drivers of the analysis.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the two schedules.

The incremental cost per QALY with the every 3 weeks schedule over the weekly schedule was $78,627. The bootstrap analysis generated a median cost per QALY of $84,989 (interquartile range: -32,060 - 198,981).

The sensitivity analysis revealed that the estimated cost per QALY was sensitive to variations in:

the difference in utility values (range of the incremental cost per QALY: 157,875 - 29,469),
the cost of irinotecan (range of the incremental cost per QALY: -65,317 - 367,526),
length of hospitalisation (range of the incremental cost per QALY: 117,198 - 40,730), and
chemotherapy administration cost (range of the incremental cost per QALY: 113,316 - 44,611).

**Authors' conclusions**
Compared with weekly irinotecan, irinotecan administered once every 3 weeks was associated with a cost-utility ratio comparable to many commonly accepted medical interventions. The base-case result was very sensitive to the cost of irinotecan.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators reflected the two irinotecan schedules that were investigated in the clinical trial. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a published clinical trial, which was valid for the study question. Power calculations were carried out to justify the sample size. The two arms of the trial were comparable at baseline. Limited information on the design of the study was reported, although the internal validity of the study was likely to have been high due to the robust characteristics of the trial.

**Validity of estimate of measure of benefit**
The use of QALYs as the summary benefit measure was appropriate as they incorporated the impact of the intervention on life expectancy and quality of life. Both dimensions were relevant aspects of care for patients with metastatic colon cancer. The source of the utility values was reported. Discounting was not relevant because of the short timeframe. QALYs are comparable with the benefits of other health care interventions.

**Validity of estimate of costs**
The authors stated explicitly the perspective adopted in the study. A detailed breakdown of the cost items was provided, although the unit costs were not presented separately from the quantities of resources used for all items. The source of the data was provided. Statistical analyses were carried out to deal with the skewed distribution of the costs. The impact of potential baseline factors on the estimated costs was also investigated. The price year was reported, which enhances the possibility of reflating the results of the analysis in other settings. Cost-to-charge ratios were used to derive the true costs of the services. The authors noted that while resource use data were gathered from all patients included in the study, a small sub-group of patients was used to derive the cost data.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the authors stressed that their results may not be generalisable to patients treated in the community. Some sensitivity analyses were carried out, which partially enhances the external validity of the analysis.

**Implications of the study**
The study results supported the use of a once every 3 weeks schedule of irinotecan. The authors stated that, as the base-case results of the analysis were sensitive to the high cost of irinotecan, the cost-effectiveness of irinotecan will probably improve when irinotecan comes off patent in 2007.
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Other publications of related interest


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