An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer
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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 drug therapies for the treatment of advanced colorectal cancer were studied: a combination of 5-fluorouracil (5FU) and leucovorin (LV), administered as the Mayo regimen (425 mg/m² 5-FU and 20 mg/m² LV for 5 days every 4-5 weeks, (5FU+LV)), and Tomudex (raltitrexed), administered as an intravenous infusion at a dose of 3 mg/m² once every 3 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients suffering from advanced colorectal cancer. Specific inclusion criteria were not reported.

Setting
The setting was hospital. The economic study was carried out in The Netherlands.

Dates to which data relate
The dates during which effectiveness evidence and resource use data were gathered were not reported. The price year was not indicated.

Source of effectiveness data
The effectiveness data were derived from a single study, which was published elsewhere, therefore limited details were reported in the present study.

Link between effectiveness and cost data
The costing was not undertaken on the same patient sample as that used in the effectiveness analysis, but was conducted retrospectively (after the effectiveness results were known).

Study sample
The total number of subjects participating in the study was 439; 216 in the 5FU+LV group and 223 in the raltitrexed group. Data on the effectiveness were available only for 212 patients treated with 5FU+LV and for 220 patients treated with raltitrexed.
Study design
The study was a multinational, open, randomised, clinical trial. Estimated average follow-up was 317 days for patients in the 5FU+LV group and 322 days for subjects in the raltitrexed group.

Analysis of effectiveness
The basis of the effectiveness analysis (intention to treat or treatment completers only) was not reported. The analysis assessed median survival, survival after 6 months and after 1 year, percentage of patients without adverse events (such as leucopenia, mucositis, WHO grade 3 and 4 anaemia, or episodes of severe asthenia), and resources used for episodes of adverse events. Data on quality of life were also collected. The comparability of the groups was not reported.

Effectiveness results
The effectiveness results were as follows:

median survival was 10.1 for patients treated with raltitrexed and 10.2 months for patients treated with 5FU+LV;
the rate of survival after 6 months was 72.07% in the raltitrexed group and 67.92% in the 5FU+LV group;
the rate of survival after 1 year was 44.14% in the raltitrexed group and 43.87% in the 5FU+LV group; and
the percentage of patients without side effects was 72.97% in the raltitrexed group and 57.08% in the 5FU+LV group.

Only the difference in the number of patients free of side effects was statistically significant.

The resources used for mucositis and leucopenia were statistically lower in the raltitrexed group compared to the 5FU+LV group (3.15% versus 21.23% for mucositis and 14.41% versus 29.72% for leucopenia), whereas the percentages of resources used for anaemia and asthenia were statistically lower in the 5FU+VL group than in the raltitrexed group (2.36% versus 9.01% for anaemia and 1.89% versus 5.85% for asthenia).

Differences in quality of life data did not reach statistical significance.

Clinical conclusions
The effectiveness analysis indicated that the two drug therapies were equivalent in terms of survival, but differed significantly in terms of side effects, which were more frequent in the group of patients treated with 5FU+VL than in the group of raltitrexed. In particular, raltitrexed was associated with less episodes of mucositis and leucopenia, but far more frequent cases of anaemia and asthenia in comparison with 5FU+VL.

Measure of benefits used in the economic analysis
The benefit measures were derived from the effectiveness analysis: survival at 6 and 12 months, and percentage of patients free of side effects. However, since no statistically significant difference was found in terms of survival, the main benefit measure was the rate of patients without side effects.

Direct costs
Discounting was not relevant due the short time horizon of the study. Unit costs and quantities of resource use were reported separately. The resource/cost boundary was not clearly reported. The analysis of costs included regimen-related components, such as medication (raltitrexed or 5FU+VL), drug administration (raltitrexed, 5FU+VL, days, and trips from and to the hospital), scheduled follow-up tests (haematology, biochemistry, and trips to the hospital), and non-regimen-related components, such as side effects, intensive care unit (ICU) days, ward days, outpatient visits, general practitioner (GP) visits, computed tomography (CT) scans, X-ray, and trips. Total costs per patient were calculated. However, in a further specification of the model, costs per patient in relationship to side effects were also computed through a regression analysis to assess the impact of occurrence of side effects on total costs: these cost estimations may
include the direct costs of treating the adverse events as well as the costs indirectly related to such events. The estimation of costs and quantities was based on actual data. Resources were mainly obtained from the trial, whereas cost data were derived from the Dutch Institute for Medical Technology. Drug prices were obtained from the Dutch pharmaceutical price list. The dates during which the data for the resource use were gathered were not reported. The price year was not indicated.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

**Indirect Costs**
Indirect costs were not included in the main analysis. However, the authors estimated the time spent by patients and their families travelling to and from the hospital ($43 per visit).

**Currency**
US dollars ($). Dutch guilders (Dfl) were converted into US dollars ($) at the following exchange rate: Dfl 1.93 = $1.

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
The rate of survival after 6 months was 72.07% in the raltitrexed group and 67.92% in the 5FU+LV group.

The rate of survival after 1 year was 44.14% in the raltitrexed group and 43.87% in the 5FU+LV group.

The rate of patients without side effects (as obtained from the effectiveness analysis) was 72.97% in the raltitrexed group and 57.07% in the 5FU+VL group.

**Cost results**
With respect to the drugs, raltitrexed cost $3,132 per patient and 5FU+LV cost $681 ($119 for 5FU and $552 for LV).

Drug administration cost $778 for raltitrexed and $2,774 for 5FU+LV.

Costs for scheduled follow-up amounted to $373 for raltitrexed and to $370 for 5FU+LV.

Costs of regimen-related components were $4,273 for raltitrexed and $3,815 for 5FU+LV.

Costs per patient for non-regimen-related components were $1,819 for raltitrexed and $1,651 for 5FU+LV.

Total costs per patients were $6,092 for raltitrexed and $5,466 for 5FU+LV, and the difference was statistically significant.

The regression analysis showed that costs associated with mucositis, leucopenia, anaemia, and asthenia were as follows: raltitrexed group: mucositis $17, leucopenia $206, anaemia $210, and asthenia $44; 5FU+LV group: mucositis $113, leucopenia $424, anaemia $55, and asthenia $14.

**Synthesis of costs and benefits**
Costs and benefits were combined by performing an incremental cost-effectiveness analysis. The additional cost of
raltitrexed over 5FU+LV per additional survivor after 6 and 12 months was $15,086 and $154,611, respectively. The additional cost of raltitrexed over 5FU+LV per additional patient free of side effects was $3,936 (95% CI: $297 - $10,560).

Authors’ conclusions
The authors concluded that the drug therapies did not differ with respect to effectiveness. On the cost side, raltitrexed was associated with higher costs than the traditional chemotherapeutic intervention, mainly due to the high acquisition costs of the drug. However, about 80% of this cost was compensated by a decrease in the costs of drug preparation, hospitalisation, and costs of travelling to and from hospital. Overall, although 5FU+LV was slightly more cost-effective, raltitrexed presented an advantage because it entailed a more convenient dosing schedule, which was preferred by the patients and which was associated with a consequently smaller number of administration visits. This would in turn result in a reduction in the overall costs, if indirect costs, as assessed by the authors, were included in the analysis.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was explicitly justified by the authors; 5FU+LV represented the standard intervention for patients suffering from advance colorectal cancer while raltitrexed was the newer drug available in the market. The authors pointed out that different dosages of 5FU+LV were available other than the Mayo regimen (i.e. the Bologna regimen, 600 mg/m² 5-FU and 200 mg/m² LV once a week, and a weekly bolus schedule, 425 mg/m² 5-FU and 80 mg/m² 2 LV once a week), but not included in the analysis. You should assess whether they represent widely used health interventions in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was based on an open, randomised, clinical trial, carried out in several countries. The randomisation of the design should ensure the high internal validity of the trial. However, the effectiveness study was published elsewhere, therefore not many details were reported in the present paper. It appeared that the choice to include side effects in the effectiveness analysis was crucial in order to detect any statistically significant differences among the groups.

Validity of estimate of measure of benefit
The benefit measures were derived from the effectiveness analysis. Data on quality of life were gathered during the trial, but statistically significant differences between the study groups were not found, in part because of the heterogeneous population enrolled.

Validity of estimate of costs
The estimation of costs was based on Dutch data then applied retrospectively to the resource use data derived from the multinational trial. This process, as the authors highlighted, could have reduced the internal validity of the analysis. However, some tests conducted on the resources employed revealed that there were no great differences in the resource consumption, therefore the results could be easily generalised to other countries. In addition, unit costs and quantities were reported separately, thus enhancing the external validity of the analysis. And finally, the perspective of the study was not reported, although a wide range of cost items was included in the study. The price year was not indicated. These latter features limit the generalisability of the cost results to other settings.

Other issues
The authors made some interesting 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 and sensitivity analyses were not carried out. The authors acknowledged that data obtained from the trial may not represent correctly daily practice, and this was reflected in the fact that different drug regimens were available but not used as comparators in the analysis.
Implications of the study
The authors recommended considering the potential advantages of raltitrexed over standard therapy in terms of patient preferences for administration dosages, reduction of the incidence of specific side effects which are particularly difficult to be borne in patients with a limited life expectancy, and in terms of cost-savings related to the introduction of indirect costs. Further research should focus on the production of more reliable data on quality of life and different regimens of 5FU+LV.

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Other publications of related interest


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