Use of raltitrexed (Tomudex) in the management of metastatic colorectal cancer

Gastrointestinal Cancer Disease Site Group

CRD summary
This review assessing the role of raltitrexed in the management of metastatic colorectal cancer found that raltitrexed appears to have equivalent survival benefits to 5-fluorouracil plus leucovorin in people with previously untreated colorectal cancer. The authors conclude that raltitrexed is a reasonable alternative when monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is indicated. The data presented support these conclusions.

Authors' objectives
To assess the role of raltitrexed in the management of metastatic colorectal cancer.

Searching
MEDLINE (to February 2003), Cancerlit (to October 2002), the Cochrane Library (Issue 4, 2002), the proceedings of annual meetings of the American Society of Clinical Oncology (1999 to 2002), and the PDQ database were searched; the search terms were reported. Information from Zeneca Inc. was also incorporated. Full reports and abstracts were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were of primary interest, although the authors also included uncontrolled phase II studies.

Specific interventions included in the review
Studies were eligible for inclusion in the review if they involved treatment with raltitrexed. Each study used a different dose and treatment schedule; these were specified individually in the review. The most common comparator was 5-fluorouracil (5-FU) plus leucovorin.

Participants included in the review
Studies of people with metastatic colorectal cancer were eligible for inclusion. The authors did not provide any details of the characteristics of the participants.

Outcomes assessed in the review
Studies were eligible if they included data on at least one of the following outcomes: survival, progression-free survival, response rate, toxicity, symptom improvement, or quality of life. The primary outcomes of the review appear to be survival, disease progression and response rate. Adverse effects were also reported.

How were decisions on the relevance of primary studies made?
The studies were selected and reviewed by one member of the Gastrointestinal Cancer Disease Site Group and methodologists. The authors did not provide further details about how the papers were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity. This review was developed using the Practice Guidelines Development Cycle reported elsewhere (see Other Publications of Related Interest).

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The authors extracted information on the study type, number of evaluable participants in each treatment group, response rate, median time to disease progression, median survival times, measures of quality of life, and
adverse effects.

**Methods of synthesis**

How were the studies combined?
The randomised trials were pooled statistically to calculate weighted estimates of median survival time and response rate. Median survival times in each treatment arm were pooled separately and weighted by the size of the treatment arm. A random-effects model was used to obtain the pooled response rate odds ratio with 95% confidence intervals (CIs). The results from the phase II studies were reported individually. The data on quality of life and adverse effects were summarised narratively.

How were differences between studies investigated?
Differences between the studies were reported narratively. The authors did not report a formal heterogeneity analysis, although they did state that they searched for differences in baseline characteristics and in treatment administration that could have influenced the study findings.

**Results of the review**
The review included four RCTs (n=1,960) and four phase II studies (n=371; 306 evaluable).

Survival time: the pooled median survival time, based on four RCTs (n=1,965), was 10.2 months for raltitrexed and 11.2 months for 5-FU plus leucovorin.

Response rates: the pooled response rate showed no statistically significant difference between raltitrexed and 5-FU plus leucovorin (odds ratio 0.95, 95% CI: 0.76, 1.19). Four phase II studies of raltitrexed (n=306) reported response rates ranging from 24 to 56%. Two reported median survival times of 11.8 and 11.2 months.

Quality of life: quality of life data were available from three RCTs. One trial reported statistically significant benefits with raltitrexed over 5-FU plus leucovorin in quality of life dimensions at week 2, but not at weeks 5 or 15. The only significant difference in one other trial was in the impact of nausea and vomiting; this was apparently greater with raltitrexed. In the third trial, quality of life at 12 weeks was significantly worse with raltitrexed for several components, including nausea and vomiting.

Adverse effects: seven RCTs and one phase II study reported adverse effects. The preliminary results from one randomised trial (n=604) reported 12 treatment-related deaths with raltitrexed and none with 5-FU plus leucovorin. Another randomised trial (n=433), which used the Symptom Checklist, found that toxicity was significantly lower overall for raltitrexed compared with 5-FU plus leucovorin. Raltitrexed was associated with less leucopenia, oral mucositis and stomatitis compared with 5-FU plus leucovorin. People receiving raltitrexed spent fewer days receiving chemotherapy and treatment for serious toxicity. Raltitrexed was also associated with increased anaemia and elevated liver transaminases that improved with continuing treatment. Two other trials (n=227 and n=495) found similar results.

Three other randomised trials (63, 38 and 61 evaluable patients) found that the most common grade 3 to 4 adverse effects from raltitrexed were diarrhoea, anaemia, elevation of liver enzymes ALT and AST, asthenia, and nausea or vomiting. A phase II study with 176 participants drew similar conclusions.

**Cost information**
The authors reported the results of one retrospective cost comparative study that was conducted with 60 people in Canada. The overall health care costs were similar for people receiving raltitrexed or 5-FU plus leucovorin.

**Authors' conclusions**
Raltitrexed appears to have equivalent survival benefits to 5-FU plus leucovorin in people with previously untreated colorectal cancer.
CRD commentary
The research question guiding this review was relatively broad and could have been more tightly defined, although the authors did specify the inclusion criteria clearly. It was unclear whether studies in languages other than English were eligible. Apart from conference proceedings and one industry source, it appears that unpublished literature was not actively sought. It was uncertain how the information provided by the industry source was used and whether this could have introduced bias.

The authors did not report how they assessed validity. This makes it difficult to consider the overall quality of the review and the studies on which it was based.

The authors pooled the data on response rate, but they did not report a formal heterogeneity analysis. From the data presented, it is difficult to assess whether pooling was appropriate, or whether there were significant methodological or other differences between the studies. There were a number of numerical discrepancies in the report.

The data presented in this review support the authors’ conclusions. However, these should be interpreted with some caution because the authors provided limited information on the steps taken to reduce bias in the review process, or to provide reassurance that the data pooling was appropriate.

Implications of the review for practice and research
Practice: The authors stated that 5-FU plus leucovorin is the standard treatment regimen for people with previously untreated metastatic colorectal cancer in whom chemotherapy is indicated. Raltitrexed is a reasonable alternative when monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is indicated (for instance, where toxicity from 5-FU plus leucovorin is a concern, or where a more convenient administration schedule is desirable). There was insufficient evidence to draw conclusions about raltitrexed in people who progress on 5-FU plus leucovorin.

Research: The authors did not state any implications for further research. They had not identified any ongoing studies as at February 2003.

Funding
Cancer Care Ontario; Ontario Ministry of Health and Long-term Care.

Bibliographic details

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.