Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer

Meta-analysis Group in Cancer

Authors' objectives
To assess the efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer.

Searching
The authors searched the MEDLINE database (beginning in 1994 onwards, and going back 10 years), the proceedings of major congresses over the 10 years prior to publication of this review, and their own personal contacts with individual trial investigators.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which accrued patients between 1984 and 1989. Treatment duration was maintained until disease progression or severe toxicity.

Specific interventions included in the review
Fluorouracil (5-FU) by continuous intravenous infusion (CI) versus bolus administration of 5-FU. Predicted cumulative dose of 5-FU was two to three times higher in the 5-FU CI arm (200 to 700 mg/m² given continually or every 21-35 days) than in the 5-FU bolus arm (400 to 600 mg/m² given every 21-35 days). Some regimens included leucovorin (folinic acid) (15 to 20 mg/m²).

Participants included in the review
Patients diagnosed with colon or rectal cancer. The mean age of participants was 63 years and 61% were male.

Outcomes assessed in the review
Outcomes assessed were: tumour response and survival rates. Complete response (CR) and partial response (PR) criteria adopted in individual trials followed the World Health Organization (WHO) recommendations and were identical in all trials. Patients with minimal response, stable disease, or tumour progression were considered to have had no response. Duration of survival was calculated from the date of randomisation to the date of death, whatever the cause of death.

Toxicity reported in individual trials followed the WHO toxicity scale or another toxicity scale easily transposable into the WHO grading system.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state who, or how many of the reviewers, performed the data extraction. However all data were checked and discussed with all collaborators at a plenary meeting of the group.

Individual data were gathered for every randomised patient including identification number, date of randomisation,
eligibility, treatment assigned by randomisation, age at randomisation, sex, performance status according to the ECOG scale, primary tumour site (colon or rectum), prior treatment (chemotherapy or radiotherapy in metastatic areas), localisation of metastases, overall response status with the first assigned treatment, crossover to another treatment arm, second treatment arm in case of crossover, date of death or last visit, survival status, and cause of death if applicable. Investigators were also asked to include data on the main toxicities: hematologic toxicity, hand-foot syndrome, and other non-hematologic toxicities (diarrhea, nausea/vomiting, and micosis).

Methods of synthesis
How were the studies combined?
Response data were analysed using the Mantel-Haenszel method. All analyses were based on an intention-to-treat basis, without any patient exclusion.

Survival data were analysed using a stratified log-rank test and through a proportional hazards regression model. The median survival time and its 95% confidence interval (CI) were estimated using reflected intervals.

How were differences between studies investigated?
The authors performed a chi-square test for heterogeneity and also performed a logistic regression model.

Results of the review
Six RCTs were included with 1,219 participants.

Tumour response rate was higher in patients assigned to 5-FU CI than in patients assigned to 5-FU bolus (22% (CR = 3% and PR = 19%) versus 14% (CR = 2% and PR = 12%); overall OR 0.55, 95% CI: 0.41, 0.75, p = 0.0002). This was equivalent to a risk reduction of 45% with a standard error of 12%.

Median duration of tumour response was 7.1 months in the 5-FU CI arm (95% CI: 5.7, 8.5 months) and 6.7 months in the 5-FU bolus arm (95% CI: 5.7, 8.5 months).

In the group of trials that used a biochemical modulation of 5-FU by LV (2 trials) the difference between continuous 5-FU plus LV and bolus 5-FU plus LV failed to reach statistical significance (tumour response OR = 0.82, 95% CI: 0.33, 2.07).

Overall survival was also higher in patients assigned to 5-FU CI (overall hazard ratio (HR) 0.88, 95% CI: 0.78, 0.99, p = 0.04). The median survival duration was 12.1 months (95% CI: 11, 13.1 months) in the 5-FU CI group versus 11.3 months (95% CI: 10.5, 12 months) in the 5-FU bolus group. The number of patients still alive in the 5-FU CI group versus the 5-FU bolus group were, respectively, 99 versus 102 at 2 years, 39 versus 23 at 3 years, and 16 versus 6 at 4 years.

When 5-FU was modulated by LV (2 trials) overall survival did not appear to be better for patients assigned to continuous 5-FU plus LV and 5-FU bolus plus LV (HR = 1.03, 95% CI: 0.77, 1.38) which was not statistically significant.

Multivariate analysis showed that randomised treatment and performance status were the only two significant predictors of tumour response, whereas the same plus primary tumour site were independent significant predictors of survival (patients with rectal cancer did somewhat better).

Grade 3 or 4 hematologic toxicity was more frequent in patients assigned to 5-FU bolus (31% versus 4%, p < 10(-16)), whereas hand-foot syndrome was more frequent in the 5-FU CI group (34% versus 13%, p < 10(-7)).

Authors' conclusions
5-FU CI is superior to 5-FU bolus in terms of tumour response and achieves a slight increase in overall survival, even though the magnitude of the benefit is small. The advantage of 5-FU CI over 5- FU bolus is reinforced by the fact that severe hematologic toxicity is less frequent in patients who receive 5-FU CI. The hematologic toxicity is much less
important in patients who receive 5-FU CI, but hand-foot syndrome is frequent in this group of patients.

**CRD commentary**
The authors have clearly stated their research question and some inclusion and exclusion criteria. The literature search appears thorough but the authors may have missed studies published outside the United States by restricting the searches to MEDLINE. The quality of the included studies was not formally assessed. The authors have not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction, but the extracted data were discussed by the review team prior to the analysis.

The data extraction is reported in tables and text and the statistical pooling was appropriate. The authors conclusions appear to follow from the results but should be viewed with caution.

**Implications of the review for practice and research**
Practice: The authors do not state any implications for practice.

Research: The authors state that the advantage of 5-FU CI over 5-FU bolus observed in patients with advanced colorectal cancer provides a rationale to study this approach in the surgical adjuvant setting.

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