Integrated analysis of overall survival in two randomised studies comparing 5-fluorouracil/leucovorin with or without trimetrexate in advanced colorectal cancer

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Background: Two randomised studies were performed with trimetrexate (TMTX) as a biochemical modulator of 5-fluorouracil (5-FU)/leucovorin (LV) in advanced colorectal cancer (ACC), one in Europe and one in the United States. Both studies were similarly designed to detect a statistically significant difference in progression-free survival (PFS). Overall survival (OS), however, was later adopted as the primary outcome measure for approvability of agents for first-line treatment of ACC. Therefore, an integrated analysis of survival data from the European and USA trials was performed to detect a clinically relevant difference in survival.

Patients and methods: The experimental arm was identical in both studies and consisted of TMTX 110 mg/m² intravenously (i.v.) followed 24 h later by i.v. LV 200 mg/m²/5-FU 500 mg/m² plus oral LV rescue. The 5-FU dose in the control arm was 600 mg/m² in the European study and 500 mg/m² in the USA study, and the USA study was placebo-controlled. Treatment was given weekly for 6 weeks every 8 weeks.

Results: A total of 746 patients were analysed. Median OS was 13.0 months for 5-FU/LV and 14.6 months for TMTX/5-FU/LV ($P = 0.15$; Wilcoxon). Median PFS was 4.4 months and 5.4 months, respectively ($P = 0.07$; Wilcoxon).

Conclusions: The addition of TMTX to a weekly regimen of 5-FU/LV does not improve the outcome for patients with ACC.

Key words: biochemical modulation, colorectal cancer, 5-fluorouracil, leucovorin, randomised trial, trimetrexate

Introduction

Trimetrexate (TMTX) is a non-classical folate antagonist with biochemical modulating activity of 5-fluorouracil (5-FU) and leucovorin (LV) [1]. Two independent randomised studies of 5-FU/LV with or without LV in first-line treatment of advanced colorectal cancer (ACC) have been performed, one in Europe [2] and one in the United States [3]. Both studies were powered to detect a statistically significant difference in median progression-free survival (PFS) of ~80%, each requiring a comparable sample size of 300 evaluable patients. Overall survival (OS) was later added as a secondary end point in each trial. In June 1999, the USA Food and Drug Administration adopted OS as a primary outcome measure for the approval of new treatments for advanced malignant diseases. As a consequence of this change, both the European and USA trials were no longer adequately powered to detect clinically relevant differences in survival at a statistically significant level. Therefore, an integrated analysis of survival data from the European and USA trials was proposed to detect clinically relevant OS differences at a statistically significant level. Justification of an integrated analysis of survival is based on the following: (i) the change in primary outcome measures for first-line treatment of ACC was externally imposed on the programme at a time when the trials were close to completion; (ii) survival is a hard and precise end point, not subject to bias; (iii) both the European and USA trial were similar in design (i.e. had identical objectives, enrolled patient populations with similar baseline demographics, and were conducted in parallel); and (iv) the integrated analysis was prospectively proposed and defined. The only differences between the study arms were that (i) the European study was not placebo-controlled and therefore no oral LV rescue was
administered in the control arm, and (ii) the 5-FU dose in the control arm was higher in the European study than in the USA study (600 mg/m² versus 500 mg/m², respectively).

Patients and methods

Eligibility criteria were identical in both studies and have been described [2, 3]. In the European study, 364 eligible patients were randomised to either LV 200 mg/m² as a 1-h intravenous (i.v.) infusion followed directly by 5-FU 600 mg/m² as an i.v. bolus (control arm) or TMTX 110 mg/m² as a 1-h i.v. infusion followed 22–24 h later by LV 200 mg/m² as a 1-h i.v. infusion followed directly by 5-FU 500 mg/m² as an i.v. bolus and LV 15 mg orally every 6 h for seven doses, starting 6 h after 5-FU administration (experimental arm). In the USA study, 382 eligible patients were randomised to either placebo (control arm) or TMTX (experimental arm) as a 1-h i.v. infusion in both arms followed 22–24 h later by LV 200 mg/m² as a 1-h i.v. infusion followed directly by 5-FU 500 mg/m² as an i.v. bolus and LV 15 mg orally every 6 h for seven doses, starting 6 h after 5-FU administration. The schedule for follow-up was identical in both studies.

Both studies were conducted in accordance with the principles of the Declaration of Helsinki, as adopted by the 29th World Medical Assembly, Helsinki, Finland, and revised at the 48th World Medical Assembly in Somerset West, Republic of South Africa, 1996. These principles are consistent with those set forth in the International Conference on Harmonization Guidelines on Good Clinical Practice, and the current USA Code of Federal Regulations (21 CFR Parts 56 and 50) regarding the requirements for independent ethics committees and institutional review boards and protection of the rights and welfare of human subjects involved in clinical investigations.

Results

A total of 746 eligible patients were analysed for PFS and OS. Median PFS was 4.4 months for the control arm and 5.4 months for the experimental arm (Figure 1). This difference was not statistically significant ($P = 0.07$; Wilcoxon test). Median OS was also not statistically significantly different ($P = 0.15$; Wilcoxon test), with 13.0 months for the control arm and 14.6 months for the experimental arm (Figure 2).

Discussion

This integrated analysis did not show an advantage for the addition of TMTX to a schedule of 5-FU/LV, either in PFS or OS. Although both studies had a very similar study design, the outcome of the individual studies differed in that the European study showed a significant PFS benefit and a trend towards benefit in OS [2], while the USA study was negative for both end points [3]. There were no statistically significant differences in the patients’ baseline characteristics between the two studies. Several comments on the different outcome of these two studies can be made.

First, the European study was not placebo-controlled, and thus open to greater bias. The fact that the median number of cycles in both treatment arms was exactly the same in both studies, however, argues against this, as well as the fact that an independent computed tomography scan review, which was performed in the majority of patients in the European study, was not significantly different from the results as provided by the investigators.

Secondly, as a consequence of the placebo-control design of the USA study, patients in the control arm also received oral LV rescue. We consider it unlikely that these extra doses of LV may have influenced the study outcome, since there are no data from previous studies to support this, and also the results on median PFS in the control arms were comparable in both studies (4.1 months and 4.4 months, respectively).

Thirdly, the result on OS in the European study may have been influenced by a more frequent use of second-line irinotecan in its experimental arm and lower exposure to 5-FU in its control arm. The longer median OS in the USA study compared with the European study is probably caused by a ~2.5

![Figure 1. Progression-free survival.](image1)

![Figure 2. Overall survival.](image2)
times more frequent use of irinotecan in the former study, as this drug was not available for routine use during the larger accrual period of the European study, which completed accrual at an earlier time than did the USA study. The fact that the median PFS times in both studies were much more in the same range compared with the median OS times supports this view. Furthermore, it cannot be excluded that the frequent use of second-line irinotecan in the USA study has obscured a small OS benefit of TMTX.

Fourthly, the incidence of grade 3 or 4 diarrhoea in the TMTX/5-FU/LV arm was significantly higher in the USA study (41%) compared with the European study (22%). Although the percentage of patients that received loperamide did not differ between the two studies, it cannot be excluded that patients with diarrhoea in the USA study may have received a less intensive dosing of loperamide. No data on this are available. The lower median dose intensity (DI) for 5-FU in the experimental arm of the USA study (82%) compared with that in the European study (92%), while the median DI in the control arms (86% and 87%, respectively) were quite comparable, probably reflects the effect of diarrhoea on the dosing in the TMTX/5-FU/LV arm of the USA study and may therefore have negatively influenced the outcome of this study.

Fifthly, the criteria that were used for disease progression differed among the studies: in the European study, progression was defined as an increase of 25% or more in the sum of all lesions, while in the USA study, such an increase in a single lesion was sufficient for termination of the study medication. As a result, several patients were withdrawn from the USA study because one small lesion progressed while more bulky disease remained stable. Since the margins of error in measuring small lesions is known to be greater compared with larger lesions, this may have caused a suboptimal exposure to the study medication in patients. The comparable results on the median number of administered cycles as well as median PFS between the two studies does not support this, however, although a small impact of this difference in study design cannot be ruled out.

In conclusion, this integrated analysis did not demonstrate any advantage in terms of PFS or OS for the addition of TMTX to a weekly regimen of bolus 5-FU plus LV. Although some factors were identified that may have influenced the outcome of both studies, it is unlikely that TMTX/5-FU/LV at this schedule is a more effective treatment than 5-FU/LV alone for the general patient population with ACC.

References