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Phase III trial of irinotecan plus infusional 5-fluorouracil/folinic acid versus irinotecan plus oxaliplatin as first-line treatment of advanced colorectal cancer

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ABSTRACT

Purpose: To determine whether irinotecan plus oxaliplatin (mIROX) is superior to irinotecan plus infusional 5-fluorouracil, leucovorin (FUFIRI) as first-line therapy of patients with metastatic colorectal cancer (mCRC).

Patients and methods: A phase III, randomised, open-label multicentre study compared standard treatment with FUFIRI (irinotecan 80 mg/m^2, 5-fluorouracil 2000 mg/m^2, folinic acid 500 mg/m^2 weekly times 6) to mIROX using an identical schedule of irinotecan plus

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oxaliplatin 85 mg/m^2 applied on days 1, 15 and 29 of a 7-week cycle. The primary end-point was progression-free survival (PFS).

Results: A total of 479 eligible patients were randomly assigned. Progression-free survival was 7.2 months in the mIROX arm and 8.2 months in the FUFIRI arm [hazard ratio = 1.14; 95% confidence interval (CI) 0.94–1.37; $P = 0.178$]. Comparable results were also obtained for overall survival time with 19 months in the mIROX-arm and 22 months in the FUFIRI-arm (hazard ratio = 1.08, $P = 0.276$). Both regimens induced an identical objective response rate (ORR) of 41%, but disease control rate (ORR plus stable disease) was significantly greater in the FUFIRI group (81% versus 68%, $P = 0.001$). Most frequent grades 1–4 side-effects of mIROX and FUFIRI treatment were nausea (80% versus 73%) and delayed diarrhoea (79% versus 68%). Grades 3–4 toxicities were generally below 10%, except for diarrhoea which was more frequent in the mIROX-arm compared to the FUFIRI-arm (19% versus 30%, $P = 0.006$)

Conclusion: mIROX failed to show superior activity compared to high-dose 5-FU/folinic acid plus irinotecan. Due to better tolerability the combination of high-dose 5-FU/folinic acid and irinotecan remains a standard of care in first-line treatment of metastatic colorectal cancer.

1. Introduction

The introduction of irinotecan and oxaliplatin caused a major improvement in the treatment of metastatic colorectal cancer (mCRC). The combined use of 5-fluorouracil (5-FU)/folinic acid (FA) together with irinotecan or oxaliplatin not only increased remission rates but also prolonged progression-free and overall survival compared to 5-FU/FA alone.[1–3]

The combined use of irinotecan and oxaliplatin was based on three assumptions: (1) There is little overlapping toxicity between the two agents with irinotecan mainly causing diarrhoea and haematotoxicity, while neurotoxicity is dose-limiting for oxaliplatin. (2) The technical applicability of the treatment may be improved if infusional 5-FU regimens requiring pump systems can be avoided. (3) Preclinical studies demonstrated that topoisomerase-I inhibitors may potentiate the cytotoxicity of DNA-damaging agents. In this context, it was shown that SN-38, the active metabolite of irinotecan, delayed the reversion of oxaliplatin-induced DNA interstrand crosslinks causing a superadditive tumour growth reduction.[4] The pharmacodynamic potentiation was observed only at the cellular level, while plasmatic pharmacokinetic interactions were not reported.[4,5]

Substantial clinical activity of irinotecan plus oxaliplatin in the treatment of advanced colorectal cancer was supported by numerous phase I–II studies.[5–11] In patients pretreated with fluoropyrimidine-based chemotherapy, this combination induced objective response rates of 15–64% and overall survival times of 11–16 months which appeared promising compared to those previously reported.[12–14]

These results led us to combine these two active agents and to investigate mIROX as a fluoropyrimidine-free combination for first-line chemotherapy of metastatic colorectal cancer. The FUFIRI-regimen was chosen as a comparator. This regimen applies infusional 5-FU given as a weekly 24-hour infusion which appeared to be associated with better tolerability and efficacy compared to bolus-5-FU regimens such as IFL. To minimise the effects of heterogeneous second line treatment on survival and to obtain data on consecutive treatment, crossover between the two study protocols was advised in case of failure of first-line therapy.

2. Patients and methods

2.1. Study design

This study was a randomised, multicentre phase III trial to investigate the efficacy of FUFIRI versus mIROX as first-line chemotherapy in patients with metastatic colorectal cancer. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee. Regular site visits were performed. The study was funded by Aventis and Pfizer.

2.2. Patient evaluation

Patients between 18 and 75 years were eligible if they had histologically proven metastatic adenocarcinoma of the colon or rectum without prior chemotherapy for metastatic disease. Prior adjuvant chemotherapy was allowed with a treatment-free interval $\geqslant 6$ months and did not include topoisomerase I inhibitors or platinum compounds. A Karnofsky performance status $\geqslant 70\%$, adequate liver- and bone marrow function parameters and bidimensionally measurable tumour lesions were mandatory. Written informed consent was obtained from each patient. Patients were excluded in the presence of symptomatic peritoneal carcinomatosís or brain metastasis, chronic inflammatory bowel disease or bowel obstruction, intolerability of 5-fluorouracil or folinic acid, secondary malignancies (except for basal cell skin cancer or in situ carcinoma of the cervix) or known Gilbert's syndrome. Further exclusion criteria were administration of other