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Neutropaenia as a prognostic factor in metastatic colorectal cancer patients undergoing chemotherapy with first-line FOLFOX

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ABSTRACT

We retrospectively analysed 153 patients with metastatic colorectal cancer who received FOLFOX with or without bevacizumab as first-line chemotherapy. Several background characteristics and chemotherapy features (grade of neutropaenia, use of bevacizumab or irinotecan, re-introduction of FOLFOX, and tumour progression) as time-varying covariates were analysed as potential prognostic factors. Of the 153 patients, mild neutropaenia (grade 1–2) occurred in 60 patients (39%) and severe neutropaenia (grade 3–4) occurred in 46 patients (30%). The other 47 patients (31%) did not experience neutropaenia. According to a multivariate Cox model with time-varying covariates, hazard ratios (HRs) of death were 0.55 (95% confidence interval (CI), 0.31–0.98; $P = 0.044$) for patients with mild neutropaenia and 0.35 (95% CI, 0.18–0.66; $P = 0.002$) for those with severe neutropaenia. Both mild and severe neutropaenia during chemotherapy are associated with improved survival in patients with MCRC. Prospective trials are required to assess whether dosing adjustments based on neutropaenia may improve chemotherapy efficacy.

1. Introduction

Neutropaenia due to cytotoxic chemotherapy is a common type of adverse event. Severe neutropaenia predisposes to lethal infection, but it is rarely fatal because of recent improvements in supportive therapy. Neutropaenia during cytotoxic chemotherapy for several types of cancer has also been reported to be associated favourably with survival.[1–6]

A possible explanation for neutropaenia's favourable impact on survival is that it is a surrogate marker for a sufficient anti-tumour dose of cytotoxic chemotherapy. In general, recommended doses of cytotoxic agents are determined in dose-finding studies that determine toxicity profiles. Sample sizes in this study phase are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable.[7] Because of the nature of dose-finding studies, a standard dose may be insufficient for those patients with faster drug elimination times.[7] Supporting this hypothesis are several early reports on the toxicity-response relationships of cytotoxic chemotherapy used for breast cancer,[1] testicular cancer,[2] ovarian cancer[3] and lymphoma.[4]

Recently Di Maio and colleagues using pooled data from randomised controlled trials reported that neutropaenia

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(grades 1–2 or grades 3–4) during chemotherapy was associated with prolonged survival in patients with advanced non-small-cell lung cancer compared to patients who did not experience neutropaenia.[5] A similar result was also reported in gastric cancer.[6] However, the effect of chemotherapy-induced neutropaenia on clinical outcome has not yet been reported in metastatic colorectal cancer (MCRC).

In this report, we describe a retrospective analysis of patients with MCRC who were treated with the first-line chemotherapy FOLFOX, in order to evaluate any possible association between neutropaenia occurring during chemotherapy and survival.

2. Patients and methods

2.1. Patients

This was a retrospective cohort study of MCRC patients who received FOLFOX as first-line chemotherapy. Principal inclusion criteria were as follows: the presence of histologically proven, inoperable colorectal cancer; age less than 80 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; sufficient bone marrow function (neutrophil count $\geqslant 2.0\times10^9$/L, leucocyte count $\geqslant 4.0\times10^9$/L, platelet count $\geqslant 100\times10^9$/L, haemoglobin $\geqslant 9.0$ g/dL); normal liver and renal function; and no history of prior chemotherapy for advanced disease.

Between April 2005 and August 2007, 264 patients with MCRC were treated and 153 patients were identified who met the inclusion criteria. Written informed consent was obtained from all patients.

2.2. Treatment delivery

Patients received either FOLFOX-4 (consisting of a 2-h infusion of leucovorin isomers [l-LV] at 100 mg/m^2 followed by a bolus of 5-FU at 400 mg/m^2 plus a 22-h infusion of 5-FU at 600 mg/m^2 for two consecutive days every 2 weeks, with oxaliplatin 85 mg/m^2 as a 2-h infusion on day 1); or modified FOLFOX-6 (consisting of a 2-h infusion of l-LV at 200 mg/m^2 followed by a 5-FU 46-h infusion of 2400 mg/m^2 every 2 weeks, with oxaliplatin at 85 mg/m^2 as a 2-h infusion on day 1). Patients with or without bevacizumab were included. Chemotherapy was delayed until recovery for a neutrophil count $< 1.0\times10^9$/L, platelet count $< 75\times10^9$/L, or any significant persisting non-haematologic toxicity. The 5-FU bolus and infusional doses were reduced by 20% if the National Cancer Institute criteria for grade 3 common side-effects of diarrhoea, anorexia or stomatitis occurred. In case of grade 4 neutropaenia, febrile neutropaenia or grade 3–4 thrombocytopaenia, the doses for oxaliplatin and 5-FU were reduced by 20%, or the 5-FU bolus was omitted from the regimen. In cases of persistent (14-d) painful paraesthesia or functional impairment, oxaliplatin was omitted from the regimen, or chemotherapy was discontinued until recovery. Other dose adjustments were made on an individual basis. Treatment was discontinued if the tumour progressed, severe toxicity occurred or at the patient's request.

The actual dose intensity was defined as the total dose of drug delivered per unit of body surface area per time unit (mg/m^2/week). The relative dose intensity of each drug was calculated as the ratio between actual dose intensity and the scheduled dose intensity.

2.3. Evaluation of neutropaenia and supportive therapy

A complete blood cell count was performed biweekly prior to each chemotherapy cycle. Patients with treatment delay due to toxicity were followed up with weekly or more frequent blood counts. The most severe grade of neutropaenia was based on the lowest recorded neutrophil count for a given patient between the first day of FOLFOX administration and 2 weeks after the last FOLFOX cycle was administered, and was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. To evaluate neutropaenia during chemotherapy, patients were divided into three categories: neutropaenia absent (grade 0), mild (grades 1–2), and severe (grades 3–4).

The indication for using granulocyte-colony-stimulating factor (G-CSF) was not defined, but G-CSF was generally used in grade 4 neutropaenia or in febrile neutropaenia, and no use as prophylaxis was allowed.

2.4. Statistical methods

The primary end-point of this study was to evaluate the association between neutropaenia during FOLFOX treatment and overall survival, which was defined as the interval between the date of beginning FOLFOX treatment and the date of death or last follow-up.

To evaluate the impact of neutropaenia on overall survival, univariate and multivariate Cox proportional hazards modelling was applied. Therefore, a measure of association in this study was the hazard ratio (HR) along with the 95% confidence interval (95% CI). As some of the assessed characteristics varied over time, analysis was performed with or without time-varying covariates (TVCs).

Forward and backward stepwise methods were used for model building. Threshold P values for inclusion or exclusion in the model were defined as 0.10 and 0.20, respectively. Confounders considered in the uni- and multivariate analyses were age (less than 65 versus 65 or older), gender (male: 0 versus female: 1), ECOG performance status (PS) (0 versus 1), primary location of tumour (colon: 0 versus rectum: 1), disease status (recurrent: 0 versus advanced: 1), number of metastatic sites (1 versus $\geqslant$2), adjuvant chemotherapy (yes: 0 versus none: 1), serum level of alkaline phosphatase (ALP) (within normal range: 0 versus increased: 1), serum level of lactate dehydrogenase (LDH) (within normal range: 0 versus increased: 1), serum level of carcinoembryonic antigen (CEA) (within normal range: 0 versus increased: 1) and leucocyte count ($\leqslant 8.0\times10^9$/L: 0 versus $>8.0\times10^9$/L: 1).

TVCs were defined as highest grade of neutropaenia during FOLFOX treatment (1: absent versus 2: mild versus 3: severe), use of bevacizumab (yes: 0 versus none: 1), use of salvage therapy by irinotecan (yes: 0 versus none: 1), re-introduction of oxaliplatin (yes: 0 versus none: 1) and tumour progression (yes: 0 versus none: 1). Since some patients received bevacizumab as an add-on to FOLFOX after Japanese regula-