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Prognostic factors in patients with non resectable metastatic colorectal cancer in the era of targeted biotherapies: Relevance of Köhne's risk classification

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ABSTRACT

Background: Köhne's prognostic classification has been previously proposed, based on performance status, alkaline phosphatase level, number of metastatic sites and white blood cells count.
Aims: To identify prognostic factors for survival and to assess the validity of Köhne's classification, in the era of targeted biotherapies, in patients treated with chemotherapy for non resectable metastatic colorectal cancer.
Methods: A total of 290 consecutive patients were retrospectively identified in all gastroenterology units of one French county, between 2004 and 2008. Univariate and multivariate analysis for overall survival were performed using pre-treatment patient characteristics.
Results: All data were available for prognostic categorization in 133 patients. Median survival was 22.1 months. The distribution and median survival for Köhne's prognostic groups were as following: good ($n = 73$; 24.8 months), intermediate ($n = 35$; 24.2 months), and poor ($n = 25$; 7.0 months). The survival difference was significant between good and poor prognostic groups ($p < 0.01$) and between intermediate and poor prognostic groups ($p < 0.01$), but not between good and intermediate prognostic groups ($p = 0.5$). The two independent prognostic factors of survival in multivariate analysis were performance status 0/1 ($p < 0.01$) and white blood cells count $< 10 \times 10^9$/L ($p < 0.01$).
Conclusions: The relevance of Köhne's classification is questioned. A simplified score could be validated by largest studies, based on white blood cells count and performance status.

1. Introduction

The mainstay of the treatment of metastatic colorectal cancer (mCRC) has been improved during the past ten years: surgically with the improvement of metastases surgery, and medically with targeted biotherapies [1–7]. Median overall survival (OS) reached more than 20 months in most recent trials assessing biotherapy as first-line therapy [2–4,6,7]. To define baseline prognostic factors is a major stake, in order to select patients who could benefit from such aggressive therapeutic strategies. In 2002, Köhne et al. have established three prognostic groups from 3825 patients with mCRC treated with 5-fluorouracil within nineteen prospective randomized and three phase II trials [8], based on four baseline clinical and biological parameters (performance status [PS], number of metastatic sites, alkaline phosphatase [ALP] level, and white blood cell [WBC] count). Median OS in good, intermediate and poor risk groups were 14.7, 10.5 and 6.4 months, respectively. These prognostic factors have also been analyzed in patients treated with combination chemotherapies including irinotecan and oxaliplatin [9–12] and more recently in patients receiving bevacizumab [13]. Köhne's classification is widely used as stratification factors in clinical trial, but data about their utilization in common practice is scarce. The purpose of this study was to assess Köhne's classification in the era of

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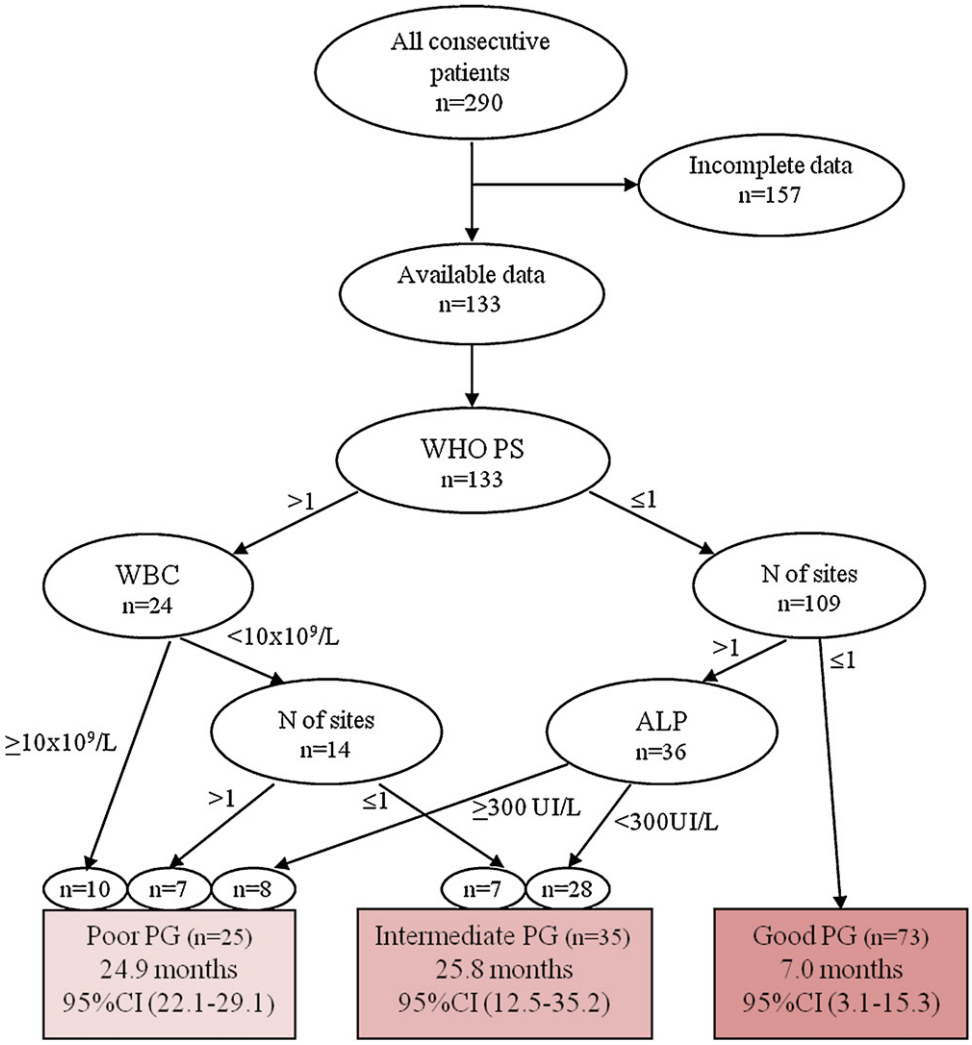

Fig. 1. Flow diagram describing initial data set, exclusions leading, and prediction model of final cohort for three Köhne's risk groups. Numbers in circles are number of patients. Split to the left denotes higher risk criterion. Numbers in shaded box are number of patients, median overall survival and 95% confidence interval in parentheses. N: number; PS: WHO performance status; WBC: white blood cell count; ALP: alkaline phosphatase Level; PG: prognosis group.

targeted biotherapies in non-selected consecutive patients with non resectable mCRC, and to identify other potential prognostic factors.

2. Patients and methods

All the six gastroenterology departments from public ($n = 4$) or private ($n = 2$) institutions authorized for the practice of chemotherapy of a French county (Marne) took part in this study. Between June 1, 2004 and June 1, 2008, consecutive patients receiving first-line chemotherapy for non resectable mCRC were retrospectively included. Patients were identified from databases of the respective six departments. The study was approved by the Institutional Review Board of Reims University Hospital.

Following clinical and biological baseline parameters (measured within the 6 weeks preceding the beginning of chemotherapy) were recorded: PS (World Health Organization (WHO) scale), number of metastatic sites, ALP level and WBC count. Other potential prognostic factors were recorded: primary tumour location, primary tumour resection, location of metastatic sites, synchronous or metachronous metastasis, platelets count (< or $\geq 400 \times 10^9$/L), haemoglobin level (< or ≥11 g/dL), lymphocytes and neutrophils levels. Data about chemotherapy regimens used were collected: type, date of first cycle, combination with targeted biotherapy (bevacizumab, cetuximab or panitumumab). All these data were collected through patients' charts review.

Statistical analyses were performed using SAS (Statistical Analysis System) software. Descriptive analysis of the population was presented as percentage, medians and 95% confidence interval (CI). Patients with missing values concerning Köhne's classification were excluded. Fischer's test for qualitative variables and Wilcoxon test for medians were used in order to compare the two populations with and without all the data. OS was measured from the date of initiation of first-line chemotherapy to the date of death from any cause or date of last news. End-point was set at October 1st, 2010. A p-value < 0.05 was considered statistically significant. OS curves were calculated using the Kaplan–Meier method. All variables were first tested by log-rank test (univariate procedure). Multivariate analysis was performed, for significant variables in univariate procedure, using the Cox model.

3. Results

A total of 290 patients were retrospectively identified from databases of the six departments. All data were available for prognostic categorization in 133 patients (Fig. 1). Baseline characteristics were similar between patients whose parameters were available ($n = 133$) vs. not ($n = 157$), except PS, which was more