European Journal of Cancer (2013) 49, 1882–1888

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.info

Taking into account successive treatment lines in the analysis of a colorectal cancer randomised trial

J. Pénichoux [a,b,c,k], S. Michiels [a,d,k], O. Bouché [e,k], P.-L. Etienne [f,k], P. Texereau [g,k], D. Auby [h,k], P. Rougier [i,k], M. Ducreux [j,k], J.-P. Pignon [a,*,k]

[a] *Biostatistics and Epidemiology Unit, Institut de Cancérologie Gustave Roussy, Villejuif, France*
[b] *Biostatistics Team, Inserm, CESP Centre for Research in Epidemiology and Population Health U1018, F-94807 Villejuif, France*
[c] *Univ Paris Sud, UMRS 1018, F-94807 Villejuif, France*
[d] *Breast Cancer Translational Research Unit, Institut Jules Bordet, Université libre de Bruxelles, Bruxelles, Belgium*
[e] *Gastrointestinal Unit, University Hospital, Reims, France*
[f] *Clinique Armoricaine, Saint-Brieuc, France*
[g] *Centre Hospitalier, Mont de Marsan, France*
[h] *Centre Hospitalier, Libourne, France*
[i] *Hôpital Européen Georges Pompidou, Paris, France*
[j] *Gastrointestinal Oncology Unit, Institut de Cancérologie Gustave Roussy, Villejuif, France*

Available online 13 March 2013

KEYWORDS
Chemotherapy
Advanced colorectal cancer
Randomised trial
Repeated events
Disease progression

Abstract The FFCD 2000–05 randomised trial included 410 patients with advanced colorectal cancer and compared a sequential arm S treated with 5-fluorouracil and leucovorin (LV5FU2) followed by FOLFOX (LV5FU2 + oxaliplatin) and then FOLFIRI (LV5FU2 + irinotecan) and a combination arm C that begins directly with FOLFOX followed by FOLFIRI. The first aim of this study was to analyse the prognostic effects on overall survival of disease progression, and of toxicities under first-line therapy. We also studied the benefit of introducing irinotecan in each arm. Finally, we compared the effect of treatment on repeated progression and toxicities. For this purpose, we used Cox regression models with time-dependent variables and shared gamma frailty regression models.

We found that early on during follow-up, the prognostic effect on survival of progression under first-line therapy was greater in C (hazard ratio [HR] = 18.0 [7.9–41.2]) than in S (HR = 7.7 [3.9–17.4]). This difference was significant, but it decreased over time. The prognostic effect of severe toxicities was greater in S (HR = 2.0 [1.4–2.9]) than in C (HR = 1.3 [0.9–1.9]). Introducing irinotecan was significantly more beneficial in S (HR = 0.2 [0.1–0.4]) than in C (HR = 0.3 [0.2–1.5]). The risk of repeated progression was not significantly different

* *Corresponding author:* Address: Service de Biostatistique et d'Epidémiologie, Institut de Cancérologie Gustave Roussy, 114, rue Edouard Vaillant, 94805 Villejuif Cedex, France. Tel.: +33 1 42 11 45 65; fax: +33 1 42 11 52 58.
E-mail address: jppignon@igr.fr (J.-P. Pignon).
[k] On behalf the FFCD 2000–05 trial investigators (for the list of its members, see Ref. 6).

0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.02.006

between the two groups (HR = 0.9 [0.8–1.1]) whereas the risk of toxicities was greater in C (HR = 1.7 [1.4–2.1]).
Overall, this study suggests that starting with less toxic first-line treatment is a valid option since it does not exert a deleterious effect on the risk of overall progression or death.

1. Introduction

Before the advent of targeted therapy, the standard regimens used to treat patients with advanced colorectal cancer were 5-fluorouracil and leucovorin (LV5FU2) combined with either oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI regimen). However, the debate continues as to whether to administer either of these combination therapies (FOLFOX or FOLFIRI) as first-line treatment because of increased toxicity compared to LV5FU2 alone.[1–4] The randomised phase III trial FFCD 2000–05 compared the efficacy of a strategy starting with LV5FU2 alone followed by second-line FOLFOX and third-line FOLFIRI (sequential group) to a strategy starting directly with FOLFOX followed by FOLFIRI (combination group).[5,6]

The primary analysis showed no significant difference in the primary end-point, progression-free survival after two lines of chemotherapy (PFS2), nor in overall survival (OS), but showed better progression-free survival after one line (PFS1) and a greater proportion of patients experiencing severe toxicity in the combination group.[6]

Firstly, this new study aimed to quantify the effects on OS of progression and toxicities occurring during first-line treatment. Secondly, the effect on OS of introducing irinotecan was estimated in each treatment group in order to ascertain whether irinotecan was introduced too late in the sequential arm. Finally, the main objective was to evaluate the overall risk of progression and toxicities, while modelling them as repeated events. This was expected to increase the statistical power. The objective of this work was not only to confirm previous results and to obtain a better understanding thereof, but also to show the interest of analyses based on repeated events in trials comparing treatment strategies across multiple lines in advanced cancer.

2. Patients and methods

Eligible patients had advanced metastatic adenocarcinoma of the colon or rectum with inoperable loco-regional disease or metastases and had not previously received systemic chemotherapy for advanced disease. Patients could have received prior adjuvant chemotherapy provided it had ended more than 6 months before entry onto the trial. Eligibility criteria are detailed elsewhere.[6] All patients gave their written informed consent to participate in the study, which was approved by the Kremlin-Bicêtre Hospital Ethics Committee.

2.1. Study design and treatment

This randomised trial was conducted by the French Federation of Digestive Oncology (FFCD 2000–05 trial). Patients were randomised between sequential and combination treatment strategies using minimisation with stratification on previous adjuvant chemotherapy, the number of invaded sites, performance status and centre.

In the *sequential group*, first-line treatment was 5FU and leucovorin, second-line treatment was FOLFOX and third-line treatment was FOLFIRI. In the *combination group*, first-line treatment was FOLFOX, second-line treatment was FOLFIRI (Fig. 1) and third-line treatment with capecitabine alone was recommended but other options (e.g. cetuximab when this drug became available in France) were allowed.

Patients in both treatment groups continued therapy until disease progression, unacceptable toxicity or until the investigator decided the patient was no longer benefiting from therapy. Breaks were not allowed except in case of toxicity during the first 6 months. Thereafter, investigators could propose treatment breaks to patients with responding or stable disease. These patients resumed the same treatment provided lesions had not progressed within the 12 weeks following the last treatment. Treatment could be delayed up to 15 days until toxicity had resolved. Dose modifications were based on the worst grades of selected toxicities in the previous cycle. Oxaliplatin was interrupted if grade 2 (or more severe) neuropathy persisted between cycles. After a period without oxaliplatin, this drug could be reintroduced if disease progressed. This was considered as the continuation of the line (first or second) and did not lead to the beginning of the next one.

2.2. Patient assessment

Tumour assessments (World Health Organization [WHO] criteria) were based on computed tomography scans (or magnetic resonance imaging) repeated every 8 weeks. Safety was assessed at least monthly until 4 weeks after the end of protocol therapy using the National Cancer Institute – Common Terminology Criteria for Adverse Events version 2.

2.3. Statistics

To assess the effect on OS of progression and severe toxicity occurring during first-line treatment, we used