Original Study

Treatment of Patients With Metastatic Colorectal Cancer in a Real-World Scenario: Probability of Receiving Second and Further Lines of Therapy and Description of Clinical Benefit

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Abstract

There are no prognostic variables indicating how many lines of therapy patients will receive and whether later lines could be effective. Among 420 subjects, joint probabilities for a patient submitted to first-line therapy to receive further lines were: second line, 74.3%; third line, 47.0%; and fourth line, 21.6%. Moreover, 31% of the patients with early progression during first-line therapy experienced a clinical benefit with later lines.

Background: The optimal therapeutic strategy for metastatic colorectal cancer patients is still a matter of debate. There are no prognostic variables indicating how many lines individual patients ought to receive, and whether later lines could be effective even when earlier ones were not. **Patients and Methods:** We retrospectively collected data from 420 consecutive patients with metastatic colorectal cancer at our institution, describing the proportion of patients who received second or later lines of therapy and the chance of a line of treatment being active when the previous line was not. For each line of treatment, we defined clinical benefit as the probability of not having had evidence of disease progression 6 months after the start of chemotherapy. **Results:** Of the 373 patients with disease progression after first-line chemotherapy (1L), 277 received a second line (2L) (probability of being submitted to a 2L (P(2L)) = 74.3%): 143 (63.3%) of 226 received a 3L (P(3L)), and 56 (45.9%) of 122 were submitted to a 4L (P(4L)). Joint probabilities were: 2L 74.3%, 3L 47.0%, and 4L 21.6%. A total of 298 (71.5%) of 417 patients had a clinical benefit with 1L; 134 (48.6%) of 276 with 2L; 50 (35.2%) of 142 with 3L; and 12 (25.0%) of 48 with 4L. Taking all these data together, 31% of the patients who experienced early progression at 1L had the chance to have a clinical benefit with any further lines. **Conclusion:** Our study demonstrated that of 4 patients submitted to a 1L, about 3 will receive a 2L, about 2 a 3L, and nearly 1 a 4L. Later lines could be beneficial even though earlier ones were not.

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Introduction

Colorectal cancer (CRC) is the second most frequently diagnosed cancer in women and the third in men, representing 12.7% and 13.2% of all cancers worldwide, respectively, with an estimate of more than 690,000 deaths in 2012.[1]

In the last 2 decades, the introduction of new and active agents have led to a progressive improvement in the overall survival of patients with metastatic CRC. Median life expectancy of patients treated with 5-fluorouracil and folinic acid, a unique therapy option in the early 1990s, was 14 months.[2] The introduction of irinotecan and oxaliplatin in the last 2 decades led to an improvement in overall survival that reached an average 21 months.[3] Finally, the description of clinical activity of targeted therapies such as bevacizumab, cetuximab, panitumumab, and more recently aflibercept, regorafenib, and ramucirumab raised the median life expectancy to > 30 months (although some of these agents have been introduced into clinical practice only very recently, and others, like ramucirumab, are not yet available in many countries).[4-10]

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The optimal therapeutic strategy is a matter of debate. Whether is better to administer front-line FOLFIRI or FOLFOX, or which targeted therapy (anti—vascular endothelial growth factor [VEGF] or anti—epidermal growth factor receptor [EGFR]) has to be administered in the first-line setting in the subgroup of patients who are in principle eligible for both has not yet been established. Moreover, the choice of the first-line therapy drives options for subsequent lines. As an example, if a patient receives FOLFIRI as front-line therapy, aflibercept could not be administered as second-line treatment because it is permitted only in patients with oxaliplatin-resistant disease. Some guidelines have recently been proposed,[11] but gray zones remain. In fact, there are no prognostic indicators that may help clinicians in determining how many chemotherapy lines a single patient will be submitted to, and there is not a sufficient degree of certainty whether the same agent (especially biologicals) administered in later lines of therapy could be as effective as those given earlier. On the other hand, it has been demonstrated that the maximal survival advantage is obtained in those patients who had had the chance to receive all the active treatments,[12] although these observations are affected by selection bias, considering that the exposition to higher number of drugs is clearly a time-dependent variable.

We collected data from metastatic CRC patients consecutively followed by the same institution from the time of first diagnosis of metastatic disease in a real-life setting. We sought to describe the proportion of patients submitted to second or further lines of chemotherapy, and to learn whether subsequent lines of therapy would result in disease control when the previous line was not beneficial.

Patients and Methods

Study Design

Clinical data and outcomes of all CRC patients treated at our institution were retrieved from our institutional database based on data prospectively collected since 1993. Data between January 1, 2003, and December 31, 2015, from patients who received first-line regimens were then extracted and entered into a new database specifically designed for the present study. The data extracted included patient demographics, performance status according to the Eastern Cooperative Oncology Group, site of primary lesion (right, from cecum to splenic flexure; left, from splenic flexure to rectum), adjuvant treatment, time of first metastasis occurrence (metachronous vs. synchronous), number of metastatic sites at the beginning of first-line treatment, date of chemotherapy start and disease progression for each line of therapy administered, and date of death or last follow-up visit.

The probability for a patient to receive each line of therapy was calculated by dividing the total number of patients submitted to that line by the number of patients who experienced disease progression while receiving the previous line. The relative probabilities were indicated as follows: P(2L) was the probability to receive a second line, P(3L) the probability to receive a third line, and P(4L) the probability to receive a fourth line. Consequently, the joint probability for a patient submitted to first-line therapy to receive a third line was $P(2L \cap 3L) = P(2L)\ P(3L)$, and the joint probability for a patient to receive a fourth line was $P(2L \cap 3L \cap 4L) = P(2L)\ P(3L)\ P(4L)$.

Table 1 Patient Characteristics

Characteristic	Value
Year of First-Line Start	
2003-2006	140 (33.3%)
2007-2010	194 (46.2%)
2011-2015	86 (20.5%)
Age (y)	
Median (range)	66 (22-84)
<70	277 (66.0%)
≥70	143 (34.0%)
Gender	
Male	249 (59.3%)
Female	171 (40.7%)
ECOG Performance Status	
0	135 (32.1%)
1	210 (50.0%)
2	56 (13.3%)
3	11 (2.6%)
Unknown	8 (2.0%)
Site of Primary Lesion	
Right	114 (27.9%)
Left	295 (72.1%)
Previous Adjuvant Treatment	
No	320 (76.2%)
Yes	100 (23.8%)
Time of First Metastasis	
Metachronous	142 (33.8%)
Synchronous	278 (66.2%)
No. of Metastatic Sites	
1	240 (57.6%)
>1	177 (42.4%)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

For each line of treatment, we defined clinical benefit as the probability of having not had evidence of disease progression 6 months after the start of chemotherapy.

Statistical Analyses

Differences between proportions were evaluated by the chi-square test with Yates correction, when appropriate. Statistical inferences of nonparametric unpaired parameters were performed with the Wilcoxon test when comparing 2 or with the Kruskal-Wallis test when comparing 3 or more variables. Survival curves were plotted by the Kaplan-Meier method and compared by the log-rank test. Overall survival was calculated from the date of diagnosis of metastatic disease until death, or censored at the last follow-up visit. For each line of therapy, progression-free survival was calculated from the date of chemotherapy start to the date of progression or death. In case of no progression, patients were censored at the date of last follow-up visit.

All statistical computations were performed by GraphPad Prism 6.0c for Mac OSX (GraphPad Software, La Jolla, CA), SPSS for Windows 22.0 (IBM SPSS, Chicago, IL), and Statistica for Windows 8.0 (StatSoft, Tulsa, OK).