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ORIGINAL RESEARCH

Combination of Irinotecan, Oxaliplatin and 5-Fluorouracil as a Rechallenge Regimen for Heavily Pretreated Metastatic Colorectal Cancer Patients

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Abstract
Purpose Our objective was to evaluate the benefit of re-exposing patients with refractory metastatic colorectal cancer (mCRC) to a combination of oxaliplatin, irinotecan and 5-fluorouracil treatment.
Methods We retrospectively analysed patients with mCRC who received a combination of oxaliplatin, irinotecan and fluorouracil as a rechallenge regimen after progressing on the same drugs. Both FOLFOXIRI and FOLFIRINOX were used. Toxicity was evaluated for each treatment cycle, and survival analysis was performed using the Kaplan-Meier method.
Results A total of 21 patients who were treated between January 2011 and December 2013 were selected for this study. Most of the patients (95.2%) had an ECOG status of 0–1. The median age at diagnosis was 52.1 years (range 36–77 years), and 14 (66.6%) patients had wild-type KRAS. Thirteen patients received FOLFIRINOX, and eight received FOLFOXIRI. Most patients had previously received at least three regimens, with 80% receiving anti-VEGF and 66% anti-EGFR antibodies. The response rate was 38%, and 24% patients had stable disease. The median time to disease progression was 4.0 months (range 1.0–9.1 months), and the median overall survival duration was 8.6 months (range 6.3–11.5 months). Most patients required dose adjustment and treatment delays. One patient experienced grade 5 neutropenic sepsis.
Conclusions Both FOLFIRINOX and FOLFOXIRI are active and potentially feasible rechallenge treatment options for heavily pretreated patients with good performance status. With dose reduction and close monitoring for toxicity, the risk of serious adverse events can be minimised.

Keywords Colorectal cancer · Refractory · Rechallenge

Introduction

Metastatic colorectal cancer (mCRC) is a highly treatable and often curable disease for which systemic therapy is the mainstay of treatment. In the 1990s, compared with the best supportive care available, 5-fluorouracil (5-FU) was the only active chemotherapy that improved survival and quality of life [1–3]. A few years later, several clinical trials demonstrated the efficacy of chemotherapy regimens containing oxaliplatin and irinotecan [4, 5]. At present, the combination of modern chemotherapy with monoclonal antibodies targeting vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) can extend patient survival to approximately 30 months [6].

Overall, patients with mCRC are living longer and have a better quality of life. However, many patients often experience disease progression after being treated with all approved drugs, but they still maintain a good performance status to tolerate further treatment, if available. The rechallenge of patients with drugs to which the tumour has already acquired resistance is generally not evaluated in clinical trials, and

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limited data are available in the literature regarding this phenomenon. Several retrospective studies have evaluated the reintroduction of a doublet chemotherapy regimen, associated with or without a monoclonal antibody, as later lines of therapy after progression on the same regimens in earlier lines. The response rates (RRs) were quite encouraging, ranging from 9.5 to 18%, with a clinical benefit (CB) in 61.9 to 83% of patients [7–9]. A recent phase II trial evaluated the safety and efficacy of reintroducing oxaliplatin in 33 patients who already progressed on this drug in earlier lines of therapy. The disease control rate after 12 weeks of treatment was 39.5%, and the RR was 6.1%, demonstrating that the reintroduction of oxaliplatin can be effective for some patients [10]. To the best of our knowledge, there are no data on the combination of irinotecan, oxaliplatin and 5-FU as a rescue regimen for heavily pretreated mCRC patients.

Based on this knowledge, we analysed the outcomes of patients who had already been treated with all available standard medications and were re-exposed to a triple-combination regimen. Our objectives were to retrospectively evaluate the benefit of re-exposing these patients to a combination of oxaliplatin, irinotecan and 5-FU and assess the tolerance, RR and median survival.

Methods

Patients

We retrospectively evaluated consecutive patients with mCRC who received FOLFIRINOX or FOLFOXIRI as a rechallenge regimen between January 2011 and December 2013 at Hospital Sírio-Libanês in São Paulo and Brasília, Brazil.

Patients were eligible for analysis if they had histologically or cytologically confirmed colorectal cancer (CRC), were 18 years or older, had radiological evidence of metastatic disease and had an ECOG status of 0–2. All patients were required to have documented progression to regimens containing oxaliplatin, irinotecan and 5-FU. Previous exposure to anti-VEGF and anti-EGFR therapies (for patients with wild-type KRAS/NRAS) was reviewed.

The data on clinical characteristics such as age, sex and performance status were obtained from medical records. We also collected information on the type of chemotherapy regimen previously administered and the best response to these treatments.

Treatment Regimen

FOLFIRINOX consists of a bolus of 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin and 400 mg/m^2 5-FU followed by 2400 mg/m^2 5-FU given as a continuous infusion for 46 h every 2 weeks. FOLFOXIRI consists of 85 mg/m^2 oxaliplatin, 165 mg/m^2 irinotecan, 200 mg/m^2 leucovorin and 3200 mg/m^2 5-FU given as a continuous infusion for 48 h every 2 weeks.

The number of cycles and the rates of dose reduction or treatment interruptions were evaluated.

Objectives and Statistical Analysis

Our primary objective was to evaluate the median overall survival (OS) of patients who received the rechallenge regimen for at least one cycle. Survival was defined as the time from the first dose of chemotherapy until death from any cause. Our secondary objective was to access toxicity, time to disease progression (TDP) and survival benefit according to KRAS status. TDP was defined from the beginning of treatment to the date when disease progression was confirmed.

OS and TDP were estimated using the Kaplan-Meier method. All statistical analyses were conducted using SPSS (version 17.0.0; Chicago, IL, USA, 2008).

Adverse events were retrospectively graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0. RR was evaluated in follow-up imaging—either computed tomography scans or magnetic resonance imaging—and retrospectively assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [11].

This study was approved by the local institutional review board and was conducted in accordance with state and federal regulations.

Results

Patient Characteristics

A total of 21 eligible patients who were treated between January 2011 and December 2013 were included in the study. The patient characteristics are described in Table 1. There were 13 men and 8 women. The median age at diagnosis was 52.1 years (range 36–77 years). Fourteen patients had wild-type KRAS, and seven had mutant KRAS. Thirteen patients received FOLFIRINOX, and eight received FOLFOXIRI as the chosen treatment regimen.

Treatment Outcomes

The majority of patients received the triplet regimen as a third line of treatment. The median number of cycles was six (range 1–11). Bevacizumab was also added to the regimen in four patients. Dose reductions were frequent: 38% of patients required a reduction in the oxaliplatin dose, 62% required a reduction in the irinotecan dose and 28% required a reduction

Table 1 Baseline patient characteristics

	Full sample (n = 21)	Wild-type KRAS (n = 14)	Mutant KRAS (n = 7)
Male	13 (61.9%)	8 (57.1%)	5 (71.4%)
Age			
Mean ± standard deviation	52.1 ± 12.3	50.4 ± 12.7	55.4 ± 11.6
(range)	(36–77)	(36–77)	(42–69)
ECOG—number (%)			
0	8 (38.1)	6 (42.9)	2 (28.6)
1	12 (57.1)	8 (57.1)	4 (57.1)
2	1 (4.8)	0 (0.0)	1 (14.3)
Previous line of therapy—median (quartiles)	5 (3–6)	4.5 (3–6)	5 (4–6)
Prior therapy—number (%)			
Fluorouracil	21 (100)	14 (100)	7 (100)
Oxaliplatin	21 (100)	14 (100)	7 (100)
Irinotecan	21 (100)	14(100)	7(100)
Cetuximab	14 (66)	14(100)	0 (0)
Bevacizumab	17 (80)	10(72)	7(100)
Best response to previous oxaliplatin—number (%)			
Complete response	1 (4.8)	1 (7.1)	0 (0)
Partial response	11 (52.4)	8 (57.2)	3 (43)
Stable disease	2 (9.5)	1 (7.1)	1 (14)
Progressive disease	7 (33.3)	4 (28.6)	3 (43)
Best response to previous irinotecan—number (%)			
Complete response	0 (0)	0 (0)	0 (0)
Partial response	15 (71.4)	13 (92.9)	2 (28.5)
Stable disease	2 (9.6)	0 (0)	2 (28.5)
Progressive disease	4 (19)	1 (7.1)	3 (43)

in the 5-FU dose. During the first cycle, only five patients received the standard dosage without any reduction in dose; the other 16 patients had the dose of at least one of the three drugs reduced.

Efficacy and Toxicity

The median OS was 8.6 months (range 6.3–11.5 months) (Fig. 1). When analysed by the KRAS status, the median OS was 6.3 months for patients with mutant KRAS and 9.3 months for patients with wild-type KRAS (Fig. 2). The median TDP was 4.0 months (range 1.0–9.1 months).

One patient experienced complete response (CR) as the best response to treatment, and seven patients experienced partial response (PR). The RR was 38%. Five patients had stable disease (SD), and eight had progressive disease (PD). CB (CR + PR + SD) was attained in 62% of the patients.

The most frequent side effects were haematological toxicity, nausea, fatigue and neuropathy. One patient experienced grade 5 toxicity due to neutropenic sepsis after cycle 1. The treatment outcomes are summarised in Table 2.

Discussion

In this retrospective analysis on heavily pretreated mCRC patients, an impressive 8.6 months of OS was achieved with rechallenge treatment combining 5-FU, oxaliplatin and irinotecan. CB was observed in 62% of patients, and the patient population generally experienced a low rate of serious adverse events. As expected [12], the patients with mutant KRAS had worse outcomes than the patients with wild-type KRAS.

Treatment of CRC has greatly advanced over the past decades, with a severalfold higher current median survival than that before the era of modern chemotherapy. However, the advances in antineoplastic therapy are still lagging, especially in developing countries where, due to regulatory reasons, there is a lack of access to some of the new agents, such as regorafenib, ramucirumab, aflibercept and TAS-102 [13–16]. Additionally, the development of resistant clones and the consequent disease progression are the major problems faced by most oncologists. Thus, in our clinical practice, we are frequently faced with patients in excellent clinical condition but no available therapies or accessible clinical trials.

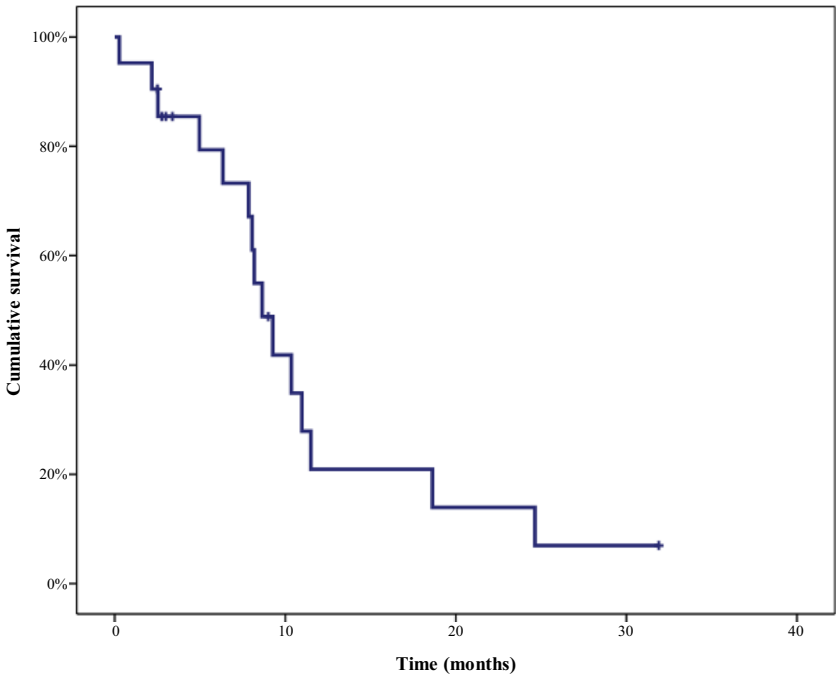

Fig. 1 Kaplan-Meier curve for overall survival

Rechallenge therapy involves the reintroduction of a therapeutic agent to which the tumour has already been shown to be resistant in previous lines of treatment [17]. The rationale behind this is that the use of a different therapy after the first progression might restore a partial sensitivity of the tumour by promoting the regrowth of sensitive clones [17]. This was demonstrated in an interesting study that explored the clonal evolution of CRC cells using circulating DNA during therapies with anti-EGFR antibodies [18]. In that study, mutant KRAS clones were detected in the patient's blood during disease progression on anti-EGFR therapy, and these clones decreased after the cessation of the anti-EGFR therapy and remained undetectable in subsequent lines [18]. In the same study, the evaluation of populations of CRC cells revealed that the patients in whom the anti-EGFR antibody was suspended regained partial sensitivity to cetuximab (an anti-EGFR antibody), while this was not observed in the patients who continued with the anti-EGFR therapy [18].

There is not enough evidence in the literature to support this strategy although some authors suggest a benefit. A retrospective, single-center study evaluated 46 patients with mCRC who received bevacizumab in combination with FOLFIRI or FOLFOX as a salvage treatment after progression on both oxaliplatin and irinotecan in previous regimens. The RR was 22% (10/46 patients), and CB was achieved in 38 patients (83%) with a median progression-free survival of 8.9 months and a median OS of 13.8 months [7]. Another retrospective study evaluated 42 patients who were treated with bevacizumab plus FOLFIRI or FOLFOX as a rechallenge regimen. The RR was 9.5%, and 22 patients (52.4%) had SD with a median OS of 9.5 months [8]. Similarly, a retrospective study evaluated the rechallenge strategy with

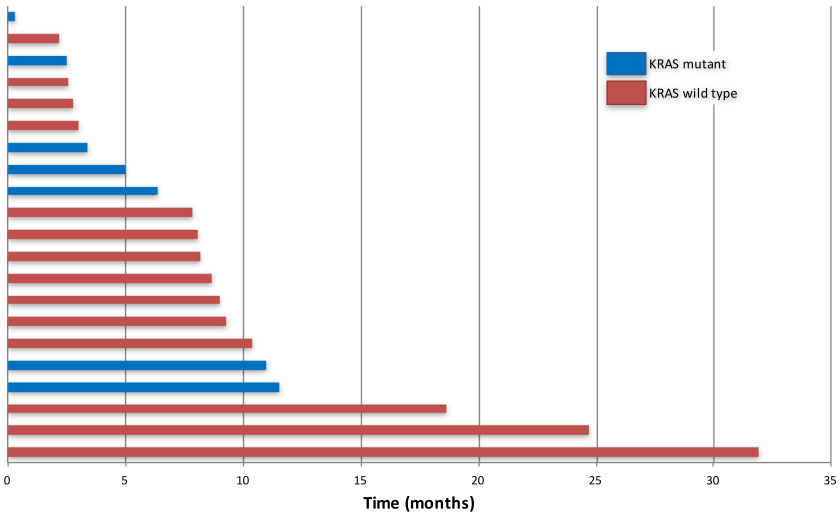

Fig. 2 Overall survival by KRAS status

Table 2 Treatment outcomes

	Full sample (n = 21)	Wild-type KRAS (n = 14)	Mutant KRAS (n = 7)
Type of regimen—number (%)			
FOLFIRINOX	13 (62)	9 (64.3)	4 (67)
FOLFOXIRI	8 (38)	5 (35.7)	3 (43)
Cycles—median (range)	5 (1–12)	5 (3–12)	6 (1–9)
Best response—number (%)			
CR	1 (5)	1 (7)	0 (0)
PR	7 (33)	4 (28.5)	3 (43)
SD	5 (24)	4 (28.5)	1 (14)
PD	8 (38)	5 (36)	3 (43)
Toxicity G3/4—number (%)			
Haematological	5 (25)	3 (21)	2 (28)
Neuropathy	4 (18)	2 (14)	2 (28)
Nausea/vomiting	7 (36)	3 (21)	4 (57)
Toxicity G5—number (%)	1 (5)	1 (7)	0 (0)
Neutropenia			
Dose adjustment—number (%)			
Oxaliplatin	8 (38)	5 (36)	3 (43)
Irinotecan	13 (62)	8 (57)	5 (71)
5-FU	6 (28)	5 (36)	1 (14)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

oxaliplatin and 5-FU in 20 patients. The RR was 18%, and 47% of the patients had SD with a median OS of 7.8 months [9]. Prospective data from studies implementing such strategies are very scarce. A recent phase II trial evaluated the reintroduction of oxaliplatin in 33 patients and demonstrated a CB of 39.5% and an RR of 6.1% after 12 weeks of treatment [10]. Another phase II trial evaluated the use of cetuximab plus FOLFIRI as a salvage regimen for patients who had progressed on the same regimen as a first-line treatment. The overall RR was 53.8% with 5.1% CR and 35.9% SD [19].

Regarding the use of triplet chemotherapy in third or subsequent lines of therapy, the only data in the literature are from a case report of a 60-year-old patient who responded to FOLFOXIRI plus bevacizumab after being considered refractory to FOLFIRI and FOLFOX [20] and a retrospective cohort study on 29 heavily pretreated patients who were subjected to a combination of intrahepatic triplet chemotherapy and bevacizumab [21]. In that cohort, patients presented mostly with hepatic cancer, which typically exhibits a more favourable biological behaviour, and the treatment was administered via hepatic arterial infusion, making it difficult to compare the results of the study with those of other studies in the literature [21].

The results of the current retrospective study are quite impressive, considering that the cohort included heavily pretreated patients. In fact, the RR of our study is higher than that of other retrospective studies that evaluated rechallenge with doublet regimens [7–9], likely because of the more intensive regimen analysed in our study. Nevertheless, it is difficult to compare different retrospective studies due to the heterogeneity of populations. Toxicity is always a concern with regards to pretreated patients, particularly when triplet chemotherapy is the chosen regimen. Most of the patients in our study required dose reductions in the first cycle, but the toxicity profile was manageable. We identified only one death due to neutropenic sepsis that was possibly related to the treatment.

We acknowledge that the retrospective design of our study has certainly led to selection bias and recognise that it is difficult to find patients in third or later lines with good performance status. Additionally, the small number of patients in our study may have contributed to a higher benefit than that expected in a larger prospective trial. Some other factors that might have influenced our results are the younger age of our patient population (mean age 52 years in the overall sample) and the fact that most of our patients had previously responded to treatment regimens containing oxaliplatin and irinotecan, which may have aided in the selection of a specific population with a more favourable disease biology and excluded those with aggressive disease and/or primary resistance to these drugs.

To the best of our knowledge, we are the first to evaluate a group of heavily pretreated patients who were rechallenged with regimens containing 5-FU, irinotecan and oxaliplatin. We demonstrated that the rechallenge approach is feasible and can result in good disease control in some patients, further delaying the progression of disease.

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Compliance with Ethical Standards

Data Availability The datasets analysed in the current study are available from the corresponding author upon reasonable request.

Conflict of Interest Gustavo dos Santos Fernandes received grants as a consultant or an advisor from Roche. Additionally, he received speaker honorarium and funding for travel, accommodations and other expenses from Roche. He also provided expert testimony on behalf of Novartis. The rest of the authors declare that they have no conflicts of interest.

Ethical Approval All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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