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The role of salvage treatment in advanced colorectal cancer

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Contents

Abstract

The selection of salvage therapy after first-line treatment failure for metastatic colorectal cancer patients has become more complex with the development of several active drugs in this setting. The addition of oxaliplatin and irinotecan to 5-fluorouracil in the first-line therapy has conditioned the election of the regimen used in second-line, becoming a standard of care the switch between both schedules at the time of disease progression. The recent introduction of new targeted drugs has complicated the scenario even more, allowing different possible combinations in first-, second-, third- and even fourth-line therapy. The role of hepatic arterial infusions has been reconsidered with the availability of new and more active cytotoxic drugs and has become an approach to be taken in mind in the management of these patients. With the possibility of active salvage therapy, surgery rescue approaches should be taken in account during all the course of the patients' disease.

Keywords: Colorectal cancer; Salvage therapy; Chemotherapy; Targeted therapy; Cetuximab; Bevacizumab

1. Introduction

Colorectal cancer (CRC) continues to be one of the most common tumour types and a leading cause of death worldwide. Recent improvements in both surgical and adjuvant chemotherapy and radiotherapy approaches have increased the survival of patients with loco-regional disease. However, despite recent advances in the treatment of metastatic disease, the prognosis of these patients remains poor.

The management of patients with metastatic colorectal cancer (mCRC) has changed dramatically over the last 5 years, with increased chances of prolonged survival. Many factors have certainly contributed to this progress, the development of new drugs being one of them. Until the mid 1990s the only available drug, with limited activity in mCRC, was 5-fluorouracil (5FU). One decade ago, the introduction of two new cytotoxic drugs, irinotecan and oxaliplatin, in addition to 5FU resulted in significant progress in the treatment of mCRC. Whereas the median life expectancy for people with this condition was in the range of 6 months without the use of any form of treatment and was extended to 10–12 months when either 5FU alone or 5FU combined with leucovorin

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Table 1
Main trials of irinotecan-based chemotherapy in second-line treatment

Study	Phase	*n*	Refractory	Schedule	RR (%)	mOS (months)
Cunninghamet al. [3]	III	189	5FU	CPT-11 vs BSC	NA	9.2 vs 6.5
Rougier et al. [4]	III	267	5FU	CPT-11 vs 5FU CI	5 vs 1	10.8 vs 8.5
Koopman et al. [5]	III	251[a]	CPC	CPT-11	10	NA
Seymour et al. [6]	III	364[b]	5FU	CPT-11 or CPT11 plus 5FU	10 vs 16	4.3 vs 4.8[c]

5FU: 5-fluorouracil, CPT11: irinotecan, BSC: best supportive care, CI: continuous infusion, CPC: capecitabine, RR: response rate, mOS: median overall survival, NA: not applicable.
[a] Only sequential arm.
[b] Only strategy A.
[c] Median progression-free survival.

(LV) was administered, the median survival was increased to 14–19 months when either irinotecan or oxaliplatin was added to a 5FU-based regimen. Survival appears to be further prolonged, around 21 months, when all three drugs are used at some point in the patients' care [1]. The availability of these new cytotoxic agents has prompted the development of different salvage chemotherapy regimens allowing the improvement of the life expectancy in this population of patients. Additionally, the development of new targeted drugs, such as cetuximab, bevacizumab and panitumumab, has also translated into a survival improvement.

In this manuscript, we aim to review the current status of second- and third-line treatments for patients with mCRC, focusing on the new opportunities that the development of new targeted drugs has generated.

2. Second-line therapy

After first-line treatment based on 5FU, oxaliplatin or irinotecan combinations several second-line options have been investigated. Approximately 50–80% of patients with mCRC receive second-line therapy [2]. These patients can generally be grouped in three categories: those who have received single agent 5FU/LV or capecitabine, those patients who have received combinations of 5FU/LV with irinotecan, and those who have received oxaliplatin-based chemotherapy. Given these options, there are a number of possible scenarios for second-line treatment. The fact that bevacizumab is being progressively included in the first-line chemotherapy schedules may substantially increase the overall survival (OS) figures, but all the discussion that is mentioned below continues to be appropriate.

In the situation of failure to 5FU in the first-line treatment of mCRC, irinotecan as a single agent was initially evaluated in two large randomized trials. The results of these trials established irinotecan as a standard second-line therapy. The first trial randomized mCRC patients to receive irinotecan or best supportive care (BSC). The results showed a statistically significant advantage in OS for the patients treated with irinotecan (1-year OS 36.2% *versus* 13.8%, $p = 0.0001$) [3]. The second trial randomized 267 patients to receive irinotecan or continuous infusion 5FU. Patients who received irinotecan lived significantly longer (1-year OS 45% *versus* 32%, $p = 0.035$) [4]. Recently, the results of two studies evaluating different sequences and combinations of chemotherapy – CAIRO and FOCUS studies – have added important pieces of information for the treatment of patients in the second-line setting [5,6]. Briefly, the CAIRO study randomized 820 patients with mCRC to receive either first-line treatment with capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin (sequential treatment arm) or first-line treatment capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin (combination treatment arm). Patients included in the sequential arm that received irinotecan single agent had a response rate (RR) of 10% after failing capecitabine [5]. The FOCUS study randomized 2135 untreated patients with mCRC to three treatment strategies: strategy A (control group) was 5FU/LV until failure, then single-agent irinotecan, strategy B was 5FU/LV until failure, then combination chemotherapy (either irinotecan- or oxaliplatin-based), and finally strategy C was combination chemotherapy from the outset (either irinotecan- or oxaliplatin-based). Patients included in this study that received irinotecan single agent or irinotecan/5FU/LV after failing 5FU/LV had a RR of 10% and 16% and a median progression-free survival (mPFS) of 4.3 and 4.8 months, respectively [6] (Table 1).

The role of oxaliplatin-based chemotherapy in second-line therapy has been evaluated by several phase II–III trials that are summarized in Table 2. The results of these trials have shown the activity of oxaliplatin in combination with 5FU/LV after failure of 5FU/LV or irinotecan-based first-line regimens [5–12]. Briefly, the RR was between 20% and 30% in those patients who had received fluoropyrimidine-based chemotherapy in the first-line setting and around 10% in those patients who had received irinotecan-based chemotherapy previously.

After 5FU failure, the combination of oxaliplatin and irinotecan has been compared with irinotecan alone in a large phase III trial. The study randomized 628 patients with mCRC in progression on first-line 5FU therapy or within 6 months after adjuvant therapy. The IROX schedule (irinotecan 200 mg/m^2 plus oxaliplatin 85 mg/m^2 every 3 weeks) showed a significant increase in median OS (mOS) (13.4 months *versus* 11.1 months, $p = 0.002$) with no significant difference in toxicity between the two arms [13].