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Methods of overcoming treatment resistance in colorectal cancer

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Contents

Abstract

Metastatic colorectal cancer remains a lethal disease with a poor prognosis in the majority of patients. Multiple drug combinations have been developed in recent years that have significantly improved response rates and overall survival however resistance to these drugs is inevitable. Novel agents are currently being developed and participation in clinical trials should be encouraged. In the absence of other treatment options in a patient with good performance status, there is compelling evidence for re-challenging with previously administered agents in different combinations. The aim of this review is to discuss mechanisms of resistance and methods to overcome treatment resistance in patients with metastatic colorectal cancer who are refractory to 5-FU, irinotecan, oxaliplatin, cetuximab and bevacizumab therapy.
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1. Introduction

Colorectal cancer is the 3rd most common cancer in males and the 2nd in females. Although overall mortality of the disease has decreased during the last decades, an estimated 1.2 million new cases and 608,700 deaths have occurred worldwide in 2008[1]. Metastatic disease at diagnosis is found in 20–25% of patients with colorectal cancer and an additional 50–60% of patients develop metastasis following initial therapy for localized disease [2,3].

Treatment for patients with metastatic colorectal cancer (mCRC) is usually palliative rather than curative. In a subset of patients with metastasis confined to liver and/or lung treatment is potentially curative with surgery. Palliative treatment in mCRC consists of systemic chemotherapy. For decades, the only agent available for the treatment of mCRC included intravenous 5-fluorouracil (5-FU) to which leucovorin (LV) was added. However, more recently new agents have been added to FU such as oxaliplatin and irinotecan. Patients on combined therapy using 5-FU/LV with irinotecan (FOLFIRI)

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demonstrated better overall survival (OS), progression free survival (PFS) and overall response (OR) compared to 5-FU/LV alone [4,5]. Similarly, better PFS and OR are achieved when 5-FU/LV is added to oxaliplatin (FOLFOX) compared to 5-FU/LV alone; however, no survival benefit has been demonstrated in randomized studies [6–8]. When comparing both FOLFOX and FOLFIRI as first line treatment in mCRC, no significant differences have been observed between these regimens [9–11]. 5-FU/LV remains a treatment option for selected patients who cannot tolerate oxaliplatin or irinotecan therapy. Patients with good performance status, progressing after first line FOLFIRI or FOLFOX, receive the alternative regimen as second-line to achieve best response and improve survival [11–15]. Irinotecan as single agent in the treatment of patients refractory to 5-FU demonstrated a clinical benefit over best supportive care and 5-FU but not over FOLFOX [16–18].

New approaches in the treatment of mCRC involved chemotherapy regimens to which novel targeted agents such as bevacizumab, cetuximab or panitumumab and more recently aflibercept and regorafenib were added. Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). Addition of bevacizumab to first line chemotherapy regimens such as FOLFOX, FOLFIRI and even 5-FU/LV demonstrated better OS, PFS and OR compared to the same treatment without bevacizumab [19–25]. Also, bevacizumab demonstrated a clinical benefit in the second-line setting in bevacizumab naïve patients [26–28]. Cetuximab is a monoclonal antibody that targets EGFR in mCRC patients whose tumors exhibit the KRAS wild type phenotype [29,30]. Some studies support the use of cetuximab in the first line treatment of mCRC in combination with chemotherapy regimens [31,32]. In patients progressing after first-line chemotherapy (oxaliplatin or irinotecan-based), cetuximab plus irinotecan showed better response rate (RR) and PFS over single agent irinotecan or cetuximab alone [33,34].

Metastatic colorectal cancer patients have several treatment lines to be considered upon progression and therapy after progression of disease depends on prior therapies received. A subset of patients progressing after receiving prior therapy with 5-FU, irinotecan, oxaliplatin, cetuximab and bevacizumab have no other treatment option to be considered but to be re-challenged with one of these prior therapies or to be treated with aflibercept or regorafenib. Fig. 1 summarizes current treatment options available for the treatment of advanced CRC.

In this review, we will discuss the mechanisms of resistance and methods to overcome treatment resistance in mCRC patients who are refractory to 5-FU, irinotecan, oxaliplatin, cetuximab and bevacizumab chemotherapy by manipulating or re-administering these drugs to patients beyond progression.

Data for this review were compiled using MEDLINE/PubMed and American Society of Clinical Oncology (ASCO) abstract databases published before February 2013. The search terms used included pretreated, overcome resistance and re-challenge in colorectal cancer. Studies in which patients did not progress on previous treatment were excluded. Only articles published in English were considered.

2. Overcoming treatment resistance in mCRC

2.1. Resistance to 5-FU

Twenty years ago, the only treatment option available for mCRC patients was 5-FU. Modulators such as LV were added to 5-FU in the 1990s that resulted in twofold higher response rates compared to bolus 5-FU alone [49,50].

At that time, patients progressing on single agent 5-FU or 5-FU/LV were treated with a higher dose of 5-FU/LV or with 5-FU ± LV as a continuous infusion (Table 1). A dose escalation of 5-FU resulted in varied RR. Weh et al. [51] reported a partial response (PR) of 9% while 2 other studies by Jager et al. [52] and Hartman et al. [53] reported higher RR (25% and 14%, respectively). The lower RR of 9% could be attributed to the patient population under study which included heavily pretreated patients (28%), patients with a poor performance status (30%) and patients with more than 2 metastatic sites (53%). Nevertheless, a higher dose was associated with some response (9–25%) and stable disease (SD) (56–61%) in previously treated 5-FU refractory patients at a time when no other second-line treatment existed. Patients who were more likely to benefit from a dose escalation were those with prior favorable response to 5-FU chemotherapy.

Other patients who were administered bolus 5-FU as first line, were treated with continuous infusion of 5-FU upon progression. Response rates are low in patients retreated with 5-FU alone (7% and 8%); however, patients receiving 5-FU + LV as continuous infusion demonstrated higher response rates of 16% and better PFS (4 months vs. 3 months) and median OS (9 months vs. 7.5 months) [54–56].

In vitro studies showed that the mechanism of resistance to bolus 5-FU is different from that of 5-FU as continuous infusion. This explains the further response achieved after progression. Short-term exposure to 5-FU is associated with RNA directed toxicity (step 3) while prolonged exposure is associated with thymidylate synthase (TS) inhibition and DNA directed toxicity (step 1 and 2) (Fig. 2). Increased levels of TS enzyme or mutation of TS have been associated with 5-FU resistance. Once resistant to short term exposure, patients receiving prolonged exposure can overcome this resistance due to the TS inhibition exerted by long term 5-FU exposure. Furthermore, LV has been shown to enhance 5-FU induced inhibition of TS and hence tumor cell kill when 5-FU exposure is long term. This further explains why patients treated with 5-FU/LV achieved better responses than patients treated with 5-FU alone [57–59].

Preclinical data suggested a synergistic action between 5-FU and irinotecan. This combination has been shown to be effective in the first line treatment of metastatic colorectal

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