Review

Maintenance Therapy in Colorectal Cancer: Moving the Artillery Down While Keeping an Eye on the Enemy

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Abstract

The survival improvement in metastatic colorectal cancer, achieved with more intensive chemotherapy regimens, has recently led clinicians to question the optimal duration of therapies and to consider the role of maintenance. Indeed, patients whose disease is controlled after induction chemotherapy may benefit from continuing a less intensive regimen in order to reinforce the results achieved with up-front treatment. In addition, the more favorable toxicity profile of maintenance approaches would ensure a better quality of life. After discussing the rationale and the difference of pursuing a maintenance strategy with chemotherapeutic and/or biologic agents, we present significant available data from the literature and comment on the current implications and future directions of maintenance therapy. The current roles of depotentiated treatment schedules, antiangiogenic compounds, epidermal growth factor receptor inhibitors, and novel targeted therapies are also reviewed. Finally, we address elements that may foster clinical and social debate on this topic, suggesting potential aspects that need to be further investigated.

Clinical Colorectal Cancer, Vol. ■, No. ■, ■-■
Keywords: Bevacizumab, Colorectal cancer, Efatutazone, EGFR inhibitors, Erlotinib, Maintenance, MGN1703, Treatment duration

Introduction

Although curative rates remain low for patients with metastatic colorectal cancer (CRC), the median overall survival (OS) is now more than 30 months in molecularly selected cases.[1,2] The introduction of irinotecan and oxaliplatin, the widespread up-front use of biologic agents, and the milestone progress achieved in molecular biology[3] have all contributed to improve outcome results to unprecedented levels.[4] In addition, with the introduction of more intensive up-front combinations including drugs with potential cumulative toxicities, the common practice of continuing first-line chemotherapy until disease progression or unacceptable toxicity has changed, raising the question of optimal treatment duration.[5] Whether first-line treatment should be continued until disease progression or discontinued as soon as a response has been achieved is debated.[6] Indeed, there is limited evidence supporting the prolongation of first-line treatment beyond 4 to 6 months,[7] and modern trials suggest avoiding treatment continuance beyond 6 months.[8] At the time of tumor reassessment, oncologists may face 3 possible scenarios. If initially unresectable disease eventually becomes resectable, patients may be referred for salvage curative surgery.[9] Conversely, if the disease has progressed, the patient may undergo second-line systemic treatment.[3] Finally, if the disease is stable or it has even shrunk yet remains unresectable, patients might be considered for maintenance therapy.[5]

Although treatment discontinuation has been addressed with perplexity, especially for those patients with optimal performance status and who experience limited cumulative adverse effects, continuing chemotherapy may cause excessive toxicity with reduced quality of life and may potentially induce drug resistance. In this landscape, maintenance therapy represents a compelling alternative, which might keep the disease under control without the intensity of a full-regimen treatment. In the quest for the optimal maintenance strategy, 2 different strategies may be considered. The first is based on the concept of intermittency; it can involve either preplanned drug holidays or clinically driven treatment breaks. The second strategy is more focused on the intensity of the treatment. In such cases,

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Submitted: Apr 19, 2015; Revised: Jul 29, 2015; Accepted: Aug 10, 2015

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1533-0028/$ - see frontmatter
http://dx.doi.org/10.1016/j.clcc.2015.08.002

maintenance includes either a depotentiated combination of the up-front therapy or a completely different compound to which the patient has not previously been exposed (Figure 1). Finally, whenever medical oncologists decide whether patients need to continue to receive treatment or can take a drug holiday, the patients' desires should always be taken into account. We completed a narrative literature review on maintenance therapy for patients with metastatic CRC, searching for eligible studies using the Medline database.

Clinical Concept of Maintenance

In patients with disease not amenable to salvage treatments, maintenance therapy aims at extending the favorable results obtained with the first-line induction therapy.[10] Drug holidays or less intensive treatments ensure less toxicity as well as fewer hospital visits with increased quality of life. Treatment breaks may also result in cost savings. Maintenance encompasses continuous maintenance, where a less-toxic part of the former regimen is used until disease progression, and switch maintenance, where patients are exposed to novel non–cross-resistant cytotoxic drugs or targeted agents that were not included in the previous induction treatment (Figure 1). Optimal candidates must have experienced disease control with the induction therapy—namely, a response, or at least disease stabilization. Consequently, the current availability of more active first-line treatments increases the number of potential candidates for maintenance therapy. Initial induction treatment followed by de-escalation of cytotoxic drugs and planned maintenance treatment is gaining credibility, and recent data in the literature suggest that maintenance treatment may play a key role in different cancer types such as lung,[11,12] breast,[13] and ovarian carcinomas.[14,15]

Cellular and Molecular Biology Underpinning Appropriateness of Maintenance Therapy

Most patients with metastatic disease experience progression, either while receiving chemotherapy as a result of intrinsic drug resistance or after an initial response as a result of an acquired drug resistance.[16-18] Understanding the cellular and molecular biology underpinning drug resistance permits improving outcomes of CRC patients and planning more effective treatment strategies. The administration of 5-fluorouracil (5-FU) with either irinotecan or oxaliplatin to fluoropyrimidine-resistant CRC cells modulates thymidylate synthase activity, implicated with the response to 5-FU treatment[19-23]; their reintroduction after disease progression is considered a rational strategy to overcome 5-FU resistance for patients initially treated with 5-FU–based combinations who had then received maintenance chemotherapy with 5-FU alone.[24,25] Accordingly, even if at the cost of higher rates of neutropenia or peripheral neuropathy, a significant response rate was observed with second-line combination regimens in clinical trials recruiting patients with 5-FU–refractory disease.[26-32]

Epidermal growth factor receptor (EGFR) signaling inhibition may resensitize tumor cells to irinotecan/SN38, leading to clinically significant effects in irinotecan-refractory CRC patients.[33-35] Similarly, cetuximab may increase the tumor response to oxaliplatin-based chemotherapy in oxaliplatin-resistant disease, reducing the activity of ERCC1, a DNA excision repair protein that mediates the removal of platinum adducts.[36,37] The use of up-front combinations including EGFR inhibitors should therefore be limited to patients with no mutations in *RAS* and possibly *BRAF* genes.[10,38-43]

Figure 1 Potential Treatment Strategies for Patients With Metastatic Disease After Up-Front Induction Treatment. *Stop After Evidence of Progressive Disease (PD), Severe Toxicity, or Patient Request. **Restart After Evidence of PD or Fixed Time