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Tumour Review

Reconsidering the benefit of intermittent versus continuous treatment in the maintenance treatment setting of metastatic colorectal cancer

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ABSTRACT

Colorectal cancer is one of the most frequent solid tumors in the western world, with low survival rates in patients with metastatic disease. Doublet chemotherapy regimens such as FOLFOX or FOLFIRI are the mainstay of standard first-line chemotherapy in the metastatic setting. The conventional treatment as a first-line approach is continuous application until progression or intolerable toxicities. However, only one third of patients are treated until progression mainly due to the side effects of chemotherapy. Notably, oxaliplatin-containing regimens such as FOLFOX/CapOx or FOLFOXIRI are associated with oxaliplatin-induced neuropathy, which is the main reason for treatment discontinuation or treatment de-escalation. On this basis, recent studies have investigated the clinical benefits of bevacizumab-based intermittent and continuous treatment regimens in the metastatic colorectal setting, together with various strategies to optimize maintenance therapy including regimens with targeted therapies, such as cetuximab, ziv-aflibercept and regorafenib. Recent studies have also investigated when maintenance therapy should be initiated as well individualizing treatment based on patient, tumor and treatment characteristics, as well as molecular biomarkers. This article reviews the current evidence for the clinical benefit of intermittent versus continuous treatment in the maintenance treatment setting of metastatic colorectal cancer, and also evaluates the effect of *RAS* and *BRAF* mutational status on maintenance strategies.

Background

Colorectal carcinoma is one of the most frequent solid tumors in the western world. With a lifetime prevalence of approximately 5%, colorectal cancer was expected to be diagnosed in about 71,830 men and 65,000 women in the United States in 2014 [1]. In the same year, an estimated 26,270 men and 24,040 women were expected to die from this disease [1]. Notably, the 5-year survival rate for patients diagnosed with metastatic colorectal cancer is low at 13% [1].

In the metastatic setting, doublet chemotherapy regimens such as FOLFOX (fluorouracil, leucovorin, oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, irinotecan) are the mainstay of standard first-line chemotherapy for metastatic colorectal cancer in patients suitable for intensive therapy [2–4]. Intensification of chemotherapy in the first-line setting has been shown to prolong progression-free survival and/or overall survival in multiple randomized trials, first with the addition of oxaliplatin or irinotecan to fluorouracil (FOLFOX/FOLFIRI) [5–7], then with the triplet regimen, FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) versus the doublet FOLFIRI [8–10]. The addition of biologic agents to FOLFOX and FOLFIRI has further improved outcomes in metastatic colorectal cancer. For example, the addition of anti-vascular endothelial growth factory therapy, such as bevacizumab, has been shown to improve progression-free survival when added to FOLFOX/XELOX in the first-line setting [11,12]. Likewise, the addition of anti-epidermal growth factor receptor (EGFR) therapy, such as cetuximab and panitumumab in patients with *RAS* wild-type tumors, have been shown to improve overall survival and/or progression-free survival when added to FOLFIRI or FOLFOX in the first-line setting, as reported in the CRYSTAL, OPUS, and PRIME studies [13–16].

The conventional treatment approach has been to continue first-line chemotherapy until disease progression or unacceptable toxicity occurs; however, in clinical practice, only one third of

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patients are treated until progression [17]. A major reason for early treatment discontinuation is the side effects of chemotherapy, which have detrimental effects on quality of life (QoL) and are a barrier to continuous chemotherapy administration [18]. Oxaliplatin-induced neuropathy/neurotoxicity in particular is one of the main limiting toxicities for most of our patients, while chronic fatigue and low-grade diarrhea are problematic with irinotecan. Oxaliplatin-induced peripheral neuropathy is associated with impaired QoL, including depressive symptoms, sleep disturbance and interference with daily activities [19], and as such, has received considerable attention. Chronic oxaliplatin-induced neuropathy is associated with a higher cumulative oxaliplatin dose, but the reported incidence varies widely [20]. For example, differences between Asian and Caucasian populations have been reported, with Asian patients showing less hypersensitivity to oxaliplatin and less susceptibility to developing oxaliplatin-induced neuropathy [21–23]. The mechanism of neuropathy is poorly understood, but is believed to involve axonal hyperexcitability resulting from oxaliplatin-mediated activation of plasma membrane ion channels in the dorsal root ganglia [24,25]. In addition, large Aβ myelinated fibers and unmyelinated C fibers are affected in colorectal cancer patients [26]. In terms of prevention of oxaliplatin-induced peripheral neuropathy, prophylaxis with infusional calcium/magnesium and venlafaxine has generally proven ineffective [25,27,28]. Other strategies including neuroprotective agents have also proven futile [29]. Such issues highlight the limitations of conventional treatment of metastatic colorectal cancer.

The patient-based advantages of intermittent chemotherapy are generally under-reported in the medical literature. However, most practitioners recognize the value to patients of having time off treatment, thereby avoiding repeated hospital attendances and allowing recovery from the continual and exhausting low-grade toxicities of long-term treatment. Intermittent treatment strategies are also less costly.

In general, more intensified chemotherapeutic regimens have demonstrated increased overall survival. This has been shown with the addition of irinotecan to fluorouracil, [7] and more recently in the TRIBE study with the addition of oxaliplatin to FOLFIRI [30]. Despite the move toward use of intensified combination regimens, several randomized trials have reported that upfront use of combination regimens not necessarily improve overall survival compared with sequential use of the same agents in advanced colorectal cancer, as seen in the CAIRO-1, FOCUS and FFCD 2000-05 studies [31–33]. For patients for whom standard full-dose intensive regimens are unsuitable, such as elderly and/or poor performance status patients, reduced dose chemotherapy may be advantageous, as noted in the FOCUS2 study [34]. Even for patients that are suitable for intensive therapy, the optimal duration and sequence of chemotherapy is unknown, and reducing the intensity of treatment may be a clinical necessity. This may be achieved by various strategies (Fig. 1), the main goal of which would be to optimize or at least sustain the benefits while minimizing toxicity. These strategies include: continuous treatment with dose reductions as needed for toxicity; a complete break in treatment after induction therapy followed by restarting treatment at progression ('stop and go'); intermittent treatment, with discontinuation of one or all drugs for a scheduled period of time; or maintenance therapy with less toxic drugs followed by re-induction at the time of disease progression [35].

The aim of this analysis is to review and reconsider the evidence for clinical benefit of intermittent versus continuous treatment in the maintenance treatment setting of metastatic colorectal cancer in the light of the recently published studies, and to evaluate the effect of *RAS* and *BRAF* mutational status on maintenance strategies.

Intermittent treatment strategies

Several studies have investigated the clinical benefits of intermittent treatment strategies in metastatic colorectal cancer patients. Randomized studies that compared continuous chemotherapy versus intermittent treatment in patients with controlled disease following induction therapy for metastatic colorectal cancer include the MRC CR06 [36], OPTIMOX1 [37], OPTIMOX2 [38], COIN [39], GISCAD [40] and CONcePT studies [41], with the OPTIMOX2 study using the same intermittent regimen as OPTIMOX1 as its control arm [38]. Key details and outcomes of these trials are summarized in Table 1. The MRC CR06 study compared intermittent versus continuous application of 5-flurouracil plus folinic acid (5-FU/FA) or raltitrexed in patients that did not progress during a 12-week induction period. The study was powered to detect a 10% difference in two-year survival rate and was not able to show any difference in OS (HR 0.87). In both arms, patients were followed up clinically every six weeks and response evaluation was done every 12 weeks. Within the population that went on drug holidays, only 37% restarted protocol treatment.

All other studies tried to address cumulative oxaliplatin toxicity by withholding oxaliplatin in the intermittent arm. Patients randomized to the 'stop and go' strategy in OPTIMOX1 received six cycles of intensified FOLFOX7 followed by 12 cycles of maintenance fluorouracil/leucovorin without oxaliplatin, then reintroduction of FOLFOX7 for another six cycles; the control group received FOLFOX4 continuously until progression or unacceptable toxicity [37]. Similarly, the intermittent arm in the CONcePT trial maintained fluorouracil/leucovorin (plus bevacizumab) with intermittent oxaliplatin [41], whereas in the COIN trial, all drugs in the intermittent arm were given on a 12-weeks-on, 12-weeks-off schedule [39]. Collectively, results from these three studies indicate that a partial 'stop and go' strategy is feasible and better tolerated than continuous chemotherapy with oxaliplatin. However, there was no clear evidence for an improvement in quality of life in these studies. An additional, small, Japanese study evaluated the feasibility of a 'stop and go' strategy with an oral fluoropyrimidine, S-1, as a maintenance therapy, administered between modified FOLFOX6 cycles [42]. It was concluded that further study was warranted, based on a reported response rate of 20.0% and disease control rate of 73.3% [42]. In accordance with findings from all of the previously-mentioned studies, a recent meta-analysis demonstrated that intermittent maintenance strategies do not result in a clinically significant reduction in overall survival compared with continuous treatment in metastatic colorectal cancer [43]. The same meta-analysis concluded that the intermittent strategy should be part of an informed discussion of treatment options with patients with metastatic colorectal cancer. However, whether an intermittent regimen is appropriate for all patients remains an open question, as a potential detrimental effect on survival cannot be excluded for some patients.

Continuous maintenance treatment

Several randomized phase III trials have evaluated continuous maintenance therapy in metastatic colorectal cancer, as shown in Table 1. Of these studies, those that compared maintenance treatment with no treatment until disease progression include OPTIMOX2 [38], CAIRO3 [44], AIO KRK 0207 [35], and SAKK 41/06 [45]. The OPTIMOX2 study demonstrated an advantage with maintenance therapy with intermittent oxaliplatin over a full treatment break, with significant improvements in the duration of disease control and median progression-free survival, but with no improvements in overall survival [38]. The results in the maintenance arm of OPTIMOX2 were comparable to those of the same