Conceptual approaches to metastatic disease

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an overlooked treatment modality?

Drug therapy for metastatic colorectal cancer has advanced dramatically over the past 20 years, with improvements in the number and effectiveness of agents at our disposal. This has created welcome opportunities to intensify treatment, improving the probability and quality of tumour response. For many patients, it has transformed a rapidly fatal terminal illness of just a few months into a chronic condition with which they will live for several years; in some cases, a potentially curable one. The role of the colorectal oncologist is now that of a strategist, making the best use of the drugs available and integrating drug therapy with other modalities—surgery, ablation, radiotherapy—to achieve the best possible outcomes for his patients.

In this article, we will focus on one treatment modality that can be an important part of this integrated oncology management strategy, bringing important benefits in quality of life, much valued by patients, and yet is often overlooked or applied in an unplanned and non-evidence-based way. So what is this treatment modality? It is time off: time off all treatment, often described as the ‘stop and go’ strategy. And like any other treatment modality, time off should be critically appraised and evaluated, compared with other treatment options in terms of the short- and long-term outcomes, and clear evidence gathered in order to inform our discussions with patients.

key decision points

Figure 1 illustrates some of the key decision points in the journey of a patient who was considered ineligible for resection of metastatic colorectal cancer. At the far left, after the initial decision to offer chemotherapy at all, the oncologist will make a choice of drugs—drawing on all available trials evidence—and on intensity of treatment: how many of the potentially active agents for that patient will be used in this first treatment episode? Several large randomized clinical trials, conducted in the ‘pre-biological’ era and reported over the past 5 years, examined the long-term impacts of more intensive or less-intensive initial therapy. Each trial included at least one arm in which initial therapy was with single-agent 5-fluorouracil (5FU) or capecitabine and this was compared with initial combination therapy. These trials produced consistent but rather unexpected results, showing that for the majority of patients a less-intensive and less-toxic initial treatment can be considered with minimal compromise to long-term survival [1, 2]. Patients with substantial cancer-related symptoms or impaired performance status (WHO) appear to benefit more from intensive initial therapy [3]; and there is general agreement that any patient who might become a candidate for curative resection after chemotherapy should be offered treatment with the highest probability of early response.

An important ‘triatage-point’ in the patient’s journey is reached after the initial period of chemotherapy—usually 3–4 months into treatment. At this point, as shown in Figure 1, there will be broadly three groups of patients. For some, typically those with limited metastatic sites and good general fitness who have responded to chemotherapy, we will be entering a ‘curative track’ including resection or ablation of metastatic sites. For others, there will have been progression through initial chemotherapy and decision will be made about second-line drug therapy or palliative care options. However, perhaps half our patients at this point will occupy the middle ground, shown in Figure 1 as ‘disease controlled but not curable’. It is this group for whom a stop-and-go treatment strategy may then be considered.

Potential approaches are illustrated in Figure 2.

- Continuous. The intention here is for the full-intensity drug regimen to be continued for as long as scans show stable disease or better and the patient tolerates it. In practice, patients on continuous therapy plans often need to reduce or stop some or all agents for reasons other than disease progression, and these range from clear, objective high-grade adverse effects through to more subjective symptoms. Patient weariness or ‘ennui’ may be a major factor and will be influenced by social and cultural factors, the oncology support services and the attitudes of the oncology team.

- Intermittent with treatment-free breaks, the so-called ‘Stop-and-go’ strategy. As shown in Figure 2, this involves stopping all anticancer drugs for periods. Crucially, patients must be carefully monitored during the treatment break, with regular clinical and radiological assessment. It is important to set clear criteria to trigger restarting the therapy. This will usually be objective signs of progressive disease (PD), but may include progression which falls short of standard PD...
criteria. An alternative approach is to use fixed breaks of 2–3 months. It is also crucially important with intermittent therapy that patients are educated and psychologically prepared—both so that they can alert the oncologist if new symptoms develop, and so that they can enjoy their period off treatment without undue anxiety. The good oncologist will help the patient to understand that progression during the break is expected and not a problem, as it will be detected in a timely way and will trigger re-starting effective therapy. It is important for the stop-and-go strategy that the detection of progression and resumption of treatment is not a 'bad news event' for the patient, but part of the planned treatment sequence.

- **Intermittent therapy with maintenance.** This strategy aims to provide periods of reduced toxicity, but with the aim that maintenance therapy will give longer breaks between episodes of full-strength therapy. The 'down side' is that patients still need regular attendances, blood tests, etc. according to the maintenance therapy used, and maintenance therapy may not be free of unwanted effects. It is therefore of course important to demonstrate that any maintenance therapy is of proven benefit over a complete treatment break, and provides tangible benefits for patients.

**treatment goals and pressures**

In considering treatment strategies, oncologists must carefully consider, and discuss with their patients, both the short- and long-term goals of treatment (Figure 3). Some patients will be prepared to trade periods of freedom from chemotherapy for small compromises in long-term survival; others may not.
Oncologists should also be careful to recognize external pressures on their treatment decisions. Are there financial or service capacity pressures to reduce chemotherapy usage; or conversely, are there financial incentives for oncologists to increase activity? Wide differences exist between patterns of cancer therapy prescribing in different health systems, and whilst individual decisions may be made with the best patient interests at heart, it is important to recognize that these ‘cultural’ differences may reflect the influence of external pressures.

Another important influence is clinical research. Over the past 10 years, regulatory authorities have increasingly accepted progression-free survival (PFS) as an end point for regulatory approval of new agents [4]. Consequently, PFS has become the commonest primary end point for trials. However, accurate measurement of PFS is not possible during intermittent treatment schedules, since there is no agreed method for dealing with the (expected, planned) progression events that occur during treatment breaks. Alternative end points such as time to failure of strategy (TFS) and duration with disease control (DDC), although more reflective of the clinical utility of treatment, have not been validated as end points for drug approval [5]. Consequently, patients participating in clinical trials may well find themselves restricted to a ‘continuous therapy’ strategy, not because it is in their best interests but because it serves the research goals. This is an important issue for regulators and clinical trial methodologists to resolve.

**trials evaluating intermittent therapy**

Several randomized trials have compared continuous and intermittent treatment strategies. The five largest reported to date are summarized in Figure 4.

The UK Medical Research Council COIN trial enrolled 2445 patients randomized equally to three arms, including a direct

![Figure 4. Randomized evaluations of intermittent chemotherapy for metastatic colorectal cancer.](image-url)
comparison of the same regimen (oxaliplatin with a ‘dealers choice’ of 5FU or capecitabine), given either continuously or intermittently with treatment-free breaks [6]. It was designed to demonstrate non-inferiority of the intermittent strategy for its primary end point, overall survival, using a stringent non-inferiority hazard ratio (HR) boundary of 1.162. Results showed a HR of 1.084 with confidence interval 1.008–1.165, crossing this boundary; thus COIN failed to show non-inferiority for intermittent therapy, and is consistent with a detriment of around 6 weeks in survival. Patients on the intermittent arm spent on average 10 weeks less on chemotherapy, had less toxicity and scored better in a wide range of quality-of-life parameters.

An interesting additional analysis of COIN compared results in patients treated at centres which adhered to the protocol and restarted >60% patients on chemotherapy after the break, or non-adherent centres where the restart rate was 33–59%. This showed that survival was not compromised by intermittent therapy at adherent centres; indeed, the best long term survival after 12 months was seen in patients on intermittent therapy at adherent centres. This result is similar to previous data from the GERCOR trial, OPTIMOX-1, showing longer survival in patients treated at centres where reintroduction of therapy was more assiduous [7].

Another COIN subgroup analysis looked for baseline factors predicting differential benefit from continuous or intermittent therapy. This showed that patients with a normal platelet count (<400 × 10^9/l) at baseline had equal survival with intermittent therapy, whilst those with thrombophilia benefited from continuous therapy. It is possible that thrombophilia, which is associated with a range of tumour activating pathways and worse overall prognosis, signals a more aggressive tumour phenotype with which treatment breaks are unsafe.

In contrast to COIN, the OPTIMOX-2 trial compared intermittent oxaliplatin with or without 5FU maintenance. It was stopped early after emergence of survival benefit for the maintenance therapy arm. However, in this small trial, a high proportion of patients had come off the study before the treatment arms diverged, making interpretation of the results difficult [8].

NORDIC VII, reported in 2012, included two arms (B and C) of continuous cetuximab plus either continuous or intermittent OxFU chemotherapy. No difference was seen in survival [9]. In a similar design, the TTD MACRO trial included continuous bevacizumab with either continuous or intermittent OxCap, and again showed no significant difference in survival [10]. Finally, COIN-B, a companion phase II study to COIN, compared intermittent/cetuximab with either treatment-free breaks or maintenance cetuximab. Some benefit was seen with cetuximab maintenance, although imbalances in the numbers of patients progressing before divergence of the treatment paths make this small trial difficult to interpret [11].

Two ongoing trials will contribute further data to the debate about intermittent therapy with or without maintenance. AIO-0207 is a three-arm trial in which intermittent oxaliplatin, fluoropyrimidine and bevacizumab is given in all arms. The randomization compares treatment-free breaks, maintenance bevacizumab or maintenance bevacizumab plus bevacizumab with either treatment-free breaks or maintenance low-dose capecitabine–bevacizumab. Similarly, CAIRO-3 is comparing intermittent OxCap–bevacizumab with either treatment-free breaks or maintenance therapy.

conclusions

Treatment breaks should be considered and discussed with patients undergoing chemotherapy for advanced colorectal cancer. Data to date suggest that most patients may take breaks from all treatment with benefit to quality of life and little or no compromise to their survival, provided they are carefully monitored and progression is treated. However, biological markers such as the platelet may help select patients with more confidence. Maintenance therapy during breaks, with low-toxicity chemotherapy or a biological agent, is of interest, but should be considered experimental at this point.

disclosure

The author has declared no conflicts of interest.

references