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Exploring the roles of combination and sequential strategies in palliative CRC care

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For over 30 years, the only approved chemotherapy for metastatic colorectal cancer (mCRC) was 5-fluorouracil (5-FU), but the situation has since changed dramatically, beginning with the European approval of irinotecan in 1995 and followed by the approval of oxaliplatin and capecitabine.[1,2] More recently, the diversity of treatments for mCRC has increased further with the availability of targeted agents, such as bevacizumab and cetuximab. While this broadening of the clinician's armamentarium heralds expectations of better outcomes for patients, it also complicates the decision-making process when considering how to best manage patients with mCRC.

Treatment decisions are based on a number of factors, which are related both to the tumour itself and to the individual patient. Resectability of the tumour, whether the patient has symptoms resulting from the tumour, and the clinical course of the disease so far are the key factors which need to be considered when determining the best course of treatment. However, patient-related factors can also have a considerable influence on the choice of therapy. The patients' attitude to their disease and desire for treatment, their age and performance status are the most important of these factors affecting the decision making process, helping the clinician to tailor the treatment approach so that it is optimal for each individual patient.[3,4]

For each individual patient, the clinician has to balance a range of determinants when arriving at a treatment decision. To illustrate of the importance of these different factors in deciding on the best course of treatment, four extreme scenarios can be considered: (1) young patients with easily resectable disease and a favourable clinical course; (2) patients for whom resection is likely to be difficult to perform but who are highly motivated; (3) patients for whom resection is not an option (either immediately or after neoadjuvant therapy), but who are relatively young and motivated, and who have symptomatic disease; and (4) elderly patients with asymptomatic disease and a fatalistic attitude towards their disease. These four scenarios raise key questions related to the choice of patient management, and illustrate how patient-related factors can modify the treatment approach.

In the first scenario involving patients with easily resectable disease, the key issue is whether to perform resection first, or to use chemotherapy to shrink the tumour prior to resection. This has been addressed in a recent study, which randomised patients with resectable liver-only metastases (n = 364) to receive either surgery alone or FOLFOX4 (5-FU, oxaliplatin plus leucovorin) for 6 cycles before and after surgery.[5]

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Perioperative FOLFOX4 chemotherapy was found to improve progression-free survival (PFS) over surgery alone by 9.2% at 3 years for patients who underwent resection, and this difference was statistically significant ($p = 0.025$). In addition, perioperative chemotherapy was well tolerated, thus suggesting that this is a good option in patients with resectable disease.

For patients with larger tumours but for whom resection could be considered (scenario 2), the issue is what is the best neoadjuvant chemotherapy to offer such patients. Regimens that have demonstrated significant activity in this setting include 5-FU/irinotecan and FOLFOX, both plus or minus biologics, as well as the triplet therapy FOLFOXIRI. Although studies to date have tended to be small in size and heterogeneous in nature, making it difficult to draw clear conclusions about the benefits of such regimens and their relative efficacies, initial results have been promising. A recent comprehensive review of the topic by Pozzo *et al.*[6] reported that resection rates of 33–56% were typically observed with a range of regimens in patients with CRC and liver metastases. Patient-related factors are also likely to have an effect on the choice of treatment, as treatment tolerability profiles vary between the regimens. Large scale, prospective studies are now required to confirm the benefit of such combination regimens, including the role of biological therapies, in patients with initially unresectable disease.

For the other two scenarios (i.e. patients with non-resectable disease) the question is what is the best palliative therapy, and how do patient-related factors influence this choice. Here the evidence is less clear cut. Although combination therapy has increasingly become the preferred first-line option in such cases in recent years, producing good response rates and PFS durations, recent studies have shown no clear overall survival (OS) benefit and a less favourable tolerability profile than planned sequential therapy using a single-agent first-line. Hence the best strategy for palliative therapy for mCRC continues to be the subject of some debate.

For combination therapy, various options are available when starting with double- or triple-agent therapy in first-line. The doublet regimens FOLFOX and FOLFIRI are well-established options for first-line therapy and are associated with a median overall survival of approximately 20 months. For example, Tournigand *et al.* reported a median OS of 21.5 months for patients receiving FOLFIRI followed by FOLFOX6 on relapse and 20.6 months for patients receiving FOLFOX6 followed by FOLFIRI on relapse.[7] CAPOX, a doublet regimen in which capecitabine is used in place of 5-FU (i.e. capecitabine/oxaliplatin), is an alternative first-line therapy that has demonstrated a similar survival benefit compared with FOLFOX.[8]

The triple chemotherapy regimen of infusional 5-FU/oxaliplatin/irinotecan (FOLFOXIRI), although not currently licensed in Europe, is another option and has recently demonstrated significant benefits over FOLFIRI.[9] In a phase III study in patients with non-resectable mCRC, FOLFOXIRI was associated with a higher confirmed response rate (60% vs. 34%, $p < 0.001$) and a higher rate of R0 resection of residual tumour metastases (15% vs. 6%, $p = 0.033$) than FOLFIRI. In addition, OS and PFS were significantly superior for FOLFOXIRI (OS, 23.6 vs. 16.7 months, $p = 0.042$; PFS, 9.8 versus 6.9 months, $p < 0.001$) and toxicities were considered manageable. The addition of a biological agent to doublet chemotherapy regimens has also demonstrated benefit.[10–13] Indeed, bevacizumab has recently been shown to lead to an OS of 28 months when combined with FOLFIRI in first-line, and has received approval for use with both oxaliplatin- and irinotecan-fluoropyrimidine combination chemotherapy regimens.[14] The benefits of combination strategies are explored further by Arnold in this supplement.[15]

Many of these patients can be expected to proceed to second- and possibly third-line therapy. Options in these settings are necessarily determined by first-line treatments. Patients who have received irinotecan-based therapy first-line can then receive FOLFOX or CAPOX second-line, followed by irinotecan/cetuximab or panitumumab (approved only in monotherapy in *KRAS* wild-type) third-line. Alternatively, such patients can receive irinotecan/cetuximab second-line, followed by FOLFOX or CAPOX third-line, but doublet chemotherapy regimens (i.e. FOLFOX and CAPOX) may well be inappropriate for use in third-line for many patients. Patients who received oxaliplatin-based therapy first-line can receive FOLFIRI second-line and irinotecan/cetuximab or panitumumab monotherapy third-line.

The number of possible alternatives for second-line (and third-line) therapy means that determining the optimal sequence and combinations of agents is difficult. To date, very few studies have compared different second-line regimens, so strategies are in large part based on their known effectiveness in first-line. However, evidence suggests that receiving fluoropyrimidine, oxaliplatin and irinotecan over the course of treatment improves survival. In an analysis of phase III studies in patients with advanced CRC, median OS correlated with the percentage of patients who received all three active drugs (oxaliplatin, irinotecan and 5-FU/FA) during their treatment, but not the percentage who received any second-line therapy.[16] Further direct comparison studies are, however, still needed to determine the optimal treatment strategies for second- and third-line therapy.

Despite the improvements in both PFS and OS seen with the above combination regimens, recent studies have provided compelling evidence for the benefits of planned sequential therapy in patients with mCRC. Fluoropyrimidine therapy (i.e. 5-FU or capecitabine) given first-line, followed by doublet chemotherapy (e.g. FOLFIRI or FOLFOX) on disease progression has proved effective in

clinical trials. Data from randomised studies comparing combination treatment with planned sequential therapy have demonstrated that the latter offers the same benefits as combination in terms of OS and quality of life and may also be better tolerated (as discussed by Seymour in this supplement [17]), although is inferior in terms of response rate and PFS. [18,19] These studies suggest that, for patients other than those who are resectable or of poor performance status, monotherapy should be considered in first-line.

Presented with strong evidence from both sides, the clinician is faced with an often difficult choice when it comes to determining the best palliative therapy for their patient. While combination regimens can be highly active, they may be more costly and expose the patient to unnecessary risk of side effects. In contrast, the individual lines of sequential therapy may be better tolerated, but produce lower response rates and reduce the proportion of patients entering later lines of therapy. In some cases, patient-related factors may make the decision relatively straightforward. So the more aggressive approach of first-line combination therapy may be appropriate for the young, motivated patient with symptomatic disease (scenario 3), while planned sequential therapy may be better suited to the elderly patient with asymptomatic disease, for whom tolerability is often a key consideration (scenario 4). For other patients, however, the best option may be far from clear cut. In each case, the optimal duration of therapy, the value of drug holidays, and the use of reduced dose maintenance strategies must also be defined. Future studies may identify specific biological markers, such as topoisomerase-1, which would allow the ready identification of those patients who would be more suited to combination or sequential treatment. [20] Until then, clinicians may agree on the value of both treatment approaches, but differ on their preferred strategy for a particular patient.

The expanding range of treatment options and the identification of molecular markers of progression and response, combined with the continuing increase in the number of colorectal cancer patients, are driving our need for improved understanding of how we use treatment options to their best advantage. In this way, we may agree on the valuable role that both approaches can have on improving the quality of care for CRC patients. This supplement reviews the data that support these two approaches and discusses the place of each strategy in the management of mCRC.

Conflicts of interest statement

Professor Sobrero has received honoraria from Merck, Pfizer, Roche, Amgen and Sanofi Aventis and has been an advisor for Merck, Roche, Sanofi Aventis, Amgen and Pfizer.

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