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Standing up for the sequential strategy

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ABSTRACT

With an increasing number of options now available for the management of metastatic colorectal cancer (mCRC), clinicians face the challenge of how to use them most effectively. First-line cytotoxic 'doublets' increase response rates and time to progression compared with monotherapy. However, five recent studies showed no significant overall survival benefit for first-line combination therapy compared with a pre-planned sequential approach starting with fluoropyrimidine monotherapy. In one trial, initial fluorouracil (FU)/irinotecan doublet therapy was superior to sequential FU then irinotecan, but the same trial showed non-inferiority for the sequential approach if a doublet was used second-line. Sub-group analyses failed to identify a subgroup benefiting from the initial doublet approach, although a trend towards benefit was seen for patients with poor performance status and some promising data suggest that predictive biomarkers may have a role in selecting the optimum strategy. The management of mCRC needs to consider the requirements of the individual patient and the whole course of treatment rather than a single line of therapy. Findings to date suggest that planned sequential therapy is a good option for many patients.

1. Introduction

For many clinicians, the question whether to use combination chemotherapy in all patients as first-line therapy for metastatic colorectal cancer (mCRC) was answered definitively and positively in 2000. In that year, four key studies were published reporting more favourable response rates and progression-free survival (PFS) for combination therapy compared with monotherapy.[1–4] Two of these trials also showed improved overall survival.[3,4] Furthermore, it was becoming apparent that some patients with inoperable liver metastases can become operable, with a possibility of cure, if first treated with a chemotherapy schedule with a high response rate.[5] Thus, in some situations at least, there was clear evidence for the therapeutic benefits of first-line combination therapy over single-agent treatment.

However, not all clinicians were convinced that this strategy should apply across the board. Combination chemotherapy is associated with significant toxicity and in some trials, despite marked improvement in initial response rate, no longer-term benefits were seen. It was apparent that second-line and subsequent therapies were an important factor. Salvage treatments had not been pre-specified in the trials, but it appeared that in trials where drugs were freely available and used in second or third line, the impact of adding the same drugs to first-line therapy was less apparent.[1,2,6] This in turn raised the question of whether pre-planned sequential therapy starting with a single agent could achieve the same overall survival benefit as the initial combination approach, but with potentially better tolerability. Here we consider the theoretical advantages of such an approach and the patients most likely to benefit from it, and review

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the data from five recent phase III trials that address this issue.

2. Initial combination or planned sequence?

In recent years oncologists and hepatic surgeons have become increasingly attuned to identifying a subset of mCRC patients who may benefit from immediate or 'interval' curative resection;[5] however, for many patients, the management of this disease is, from the outset, palliative in intent. For these patients, each anti-cancer drug which is started may be used until it fails – either through cancer progression or toxicity – but it is virtually inevitable that failure will occur at some point. At the time of failure, we may turn to other agents to regain cancer control, but since the number of effective drugs available for mCRC is limited, careful consideration needs to be given as to how they are best used to give the patient the best overall duration and quality of life.

For any two drugs, A and B, there are several ways in which they can be given (Figure 1). Both might be administered together as initial combination therapy (AB) and continued until failure. Alternatively, a sequential approach could be used, starting with a single drug, continued until failure, then either replaced with the second (A then B) or 'up-graded' to the doublet (A then AB). These different approaches – initial combination or sequential therapy – may provide different benefits.

Initial combination therapy certainly offers a higher response rate than a single agent, typically 40–50% RECIST responses with doublets compared with 20–25% for optimum single-agent fluoropyrimidine regimens. For a patient presenting with bulky disease or major symptoms this higher probability of an early response may outweigh all other considerations, but it comes at a price: the unwanted effects of treatment are undoubtedly greater, and it 'uses up' two of the three main classes of cytotoxic agent available for this disease in the first treatment episode. Given that median time to progression with combination therapy is typically only 2–3 months longer than with a single agent, might the sequential approach provide a longer period of disease control before needing to turn to third and subsequent drugs? But to rely on a single agent in first line also carries risks: if the disease is primarily resistant to that agent, will it be possible to identify progression and move on to the next treatment before symptoms develop, whilst the patient is still fit enough to receive it, and without causing psychological distress? And might treatment with an ineffective agent reduce the chance of benefit from the active one?

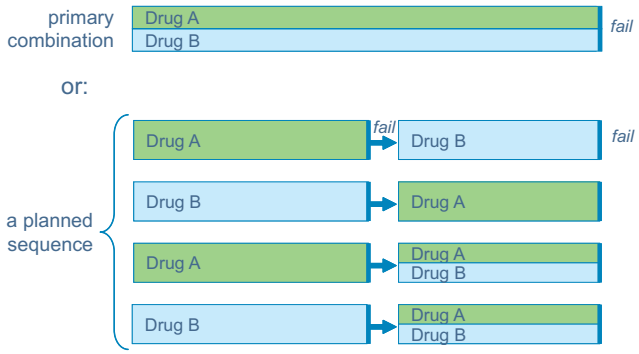

Fig. 1 – Potential scheduling options for the administration of two drugs.

Over the past three years we have seen reports from several prospective clinical trials addressing these questions. Do these trials allow us to see how the theoretical considerations translate into clinical practice?

3. Prospective studies

To date, five prospective, randomised clinical trials have been reported in which patients with non-pretreated mCRC were randomly allocated to different treatment plans which included initial 2-drug combination chemotherapy or planned sequential therapy starting with a single cytotoxic agent (Table 1).[7–11] The five trials were initiated in 2000–2003; none of them included anti-VEGF- or EGFR-targeted therapies, and all included evaluation of overall survival as either the primary or a secondary endpoint. Four were run by academic co-operative groups: the UK MRC (FOCUS[8] and FOCUS2[9]), the Dutch Colorectal Cancer Group (CAIRO[7]) and the Fédération Francophone de la Cancérologie Digestive (FFCD 2000–05[11]). The LIFE Trial[10] was sponsored and run by Sanofi-Synthelabo. At present, only FOCUS and CAIRO have been fully published.

3.1. General trial designs

All five trials involved fluoropyrimidine, oxaliplatin and irinotecan, and in each case the patients allocated to sequential therapy started with single-agent fluoropyrimidine, while initial combination therapy patients received the same fluoropyrimidine plus either oxaliplatin or irinotecan. In CAIRO, the fluoropyrimidine was oral capecitabine and FOCUS2 included a factorial randomisation between capecitabine and infusional fluorouracil/leucovorin (FU/LV), while the other three trials used FU/LV in all patients. In each trial, patients were to be treated with their allocated regimen until evidence emerged of treatment failure, at which point they would, if fit enough, move to the next prospectively-planned treatment. In each case, patients who could not, for whatever reason, receive the next planned treatment remained evaluable by intention to treat.

In three trials (FOCUS, CAIRO and FOCUS2) it was planned for patients to receive the same number of

Table 1 – Summary of studies comparing first-line combination therapy and planned sequential therapy

Study	No. of patients	Median age (years)	Patients with PS 2 (%)	First-line combination therapy	Planned sequential therapy
CAIRO [7]	803	63	4	Cap/Ir *then* Cap/Ox	Cap *then* Ir *then* Cap/Ox
FOCUS [8]	2135	64	9	FU/Ir or FU/Ox [a]	FU *then* FU/Ir or FU/Ox or Ir [a]
FOCUS2 [9]	460	75	29	FU/Ox or Cap/Ox [b]	FU or Cap *then* FU/Ox or Cap/Ox [b]
FFCD [11]	410	69	16	FU/Ox *then* FU/Ir	FU *then* FU/Ox *then* FU/Ir [c]
LIFE [10]	725	62	6	FU/Ox *then* Ir	FU *then* Ir

Cap: capecitabine; FU: infusional 5-fluorouracil; Ir: irinotecan; Ox: oxaliplatin.
[a] Optional use of Cap/Ox or Cap/Ir on failure of first-line combination therapy or second-line therapy in the sequential group, introduced half-way through the trial.
[b] Optional use of Ir on failure of first-line combination therapy or second-line therapy in the sequential group.
[c] Primary endpoint second-PFS measured before starting FU/Ir in sequential therapy group.

cytotoxic agents whichever trial arm they were allocated to. In the FFCD trial, it was planned for patients in both arms to receive three drugs, but the primary endpoint (time to second progression) was measured when patients in the sequential group had received two drugs and those in the combination arm had received three. In LIFE, the treatment plan for patients allocated to sequential therapy was just two drugs, compared with three in the combination group.

3.2. Trial details

The CAIRO (CApecitabine, IRinotecan, Oxaliplatin) trial was a 2-arm comparison of initial capecitabine therapy followed by second-line irinotecan (sequential treatment) or first-line capecitabine/irinotecan (combination treatment). [7] Both groups were then planned to receive capecitabine/oxaliplatin as third- or second-line treatment, respectively.

FOCUS (Fluorouracil, Oxaliplatin and CPT-11: Use and Sequencing) was a large trial in which the three arms were (A) sequential single agent FU/LV followed by single-agent irinotecan, (B) sequential single-agent FU/LV followed by combination chemotherapy, or (C) initial combination therapy. [8] In arms B and C a further sub-randomisation allocated patients to irinotecan/FU/LV or oxaliplatin/FU/LV as the combination therapy to be used. When FOCUS started in 2000, subsequent crossover was to be avoided, so all patients were planned to receive two drugs: FU/LV and either irinotecan or oxaliplatin, but not both. However, this design was later amended to provide 'third-drug crossover' in all arms.

FOCUS2 involved elderly and/or frail patients who had been judged unfit to receive full-dose combination chemotherapy. [9] All treatments were therefore started at 80% of standard doses and increased to standard dose after 6 weeks if well tolerated. This trial used a 2×2 factorial randomisation, comparing FU/LV versus capecitabine, and comparing initial combination fluoropyrimidine plus oxaliplatin versus sequential fluoropyrimidine followed by fluoropyrimidine/oxaliplatin combination therapy. Individuals were therefore randomised to one of four first-line treatments: infusional 5-FU or capecitabine alone, or either of these agents in combination with oxaliplatin. [9] For patients receiving first-line single-agent therapy, oxaliplatin was added to the fluoropyrimidine on treatment failure as second-line therapy. Irinotecan was available as subsequent salvage therapy in all arms.

In FFCD 2000–05, patients were randomised to two arms. [10] In the sequential arm, patients started with FU/LV, with a plan to receive combination oxaliplatin plus FU/LV (FOLFOX6) at the time of first progression, then irinotecan plus FU/LV/irinotecan (FOLFIRI) after second progression. In the initial combination arm, patients started with first-line FOLFOX6 followed by FOLFIRI at first progression. The primary endpoint of the study was set as 'second-PFS', when sequential-arm patients had received only two drugs. However, all patients were planned to receive all three drugs eventually and overall survival was also reported. [10]

LIFE (Longevity Improvement with Fluorouracil and Eloxatin) compared first-line FU/LV followed by second-line irinotecan, versus first-line FOLFOX with second-line irinotecan, i.e. a 2-drug versus a 3-drug plan. [11]

3.3. Study findings

Unsurprisingly, all five of the trials described here were consistent with other clinical data in showing higher response rates and increased PFS for the first-line combination therapy with fluoropyrimidine and oxaliplatin or irinotecan over the equivalent single-agent fluoropyrimidine treatment. It was also a consistent finding that the rates of toxicity, although felt by all investigators to be reasonable and manageable, were significantly higher with combination therapy than with single-agent fluoropyrimidines.

However, the analysis of long-term outcomes – which was the purpose of these studies – produced quite unexpected results. Contrary to expectations, the improvements in response and PFS rates with first-line combination chemotherapy did not translate into clear overall survival benefits compared with planned sequential treatment in these studies.

In the FOCUS trial, median overall survival was similar for patients receiving sequential FU/LV followed by combination therapy (15.1 months) or initial combination therapy (15.9 months); the hazard ratio (HR) for this comparison, in over 1400 patients, was 1.06 (90% CI 0.97–1.17), satisfying the pre-defined criteria for non-inferiority.[8] Overall survival was, however, reduced in those receiving sequential FU/LV followed by irinotecan monotherapy, with median 13.9 months, and this was significantly inferior to the group receiving first-line irinotecan/FU/LV in combination (HR 0.84, 95% CI 0.73–0.96, $p = 0.01$).

Given this single positive finding from FOCUS, the CAIRO trial might have been expected to show a survival advantage for the combination over sequential therapy arms, as the sequential group in CAIRO also received consecutive monotherapy (capecitabine followed by irinotecan). Interestingly, however, median overall survival in CAIRO did not differ significantly between the two groups – 16.3 months for sequential therapy and 17.4 months for the combination (HR 0.92, 95% CI 0.79–1.08, $p = 0.33$).[7] Similarly, in FOCUS2, overall survival showed no significant difference between the sequential therapy and initial combination groups (HR 0.97, $p = 0.75$) although, as in all these trials, response rates were significantly higher in patients receiving first-line combination ($p < 0.0001$).[9]

The other two trials – FFCD and LIFE – were particularly likely to have shown advantages for the first-line combination treatment over sequential therapy since in these trials, at the time of the primary endpoint (second-PFS in FFCD, overall survival in LIFE), patients allocated to sequential therapy were to have been exposed to two drugs whilst the combination group was to have received three.[10,11] However, both trials were in fact negative. In the FFCD study, both the second-PFS primary endpoint and overall survival were similar in the two treatment groups, with HR = 0.92 ($p = 0.43$) and HR = 1.05 ($p = 0.67$), respectively.[10] And in the LIFE trial, the 'longevity improvement' anticipated in its title was not in the end seen: median overall survival did not differ significantly between sequential treatment and first-line combination therapy (median 15.2 vs. 15.9 months, HR = 0.93, $p = 0.155$).[11]

4. Treatment strategies – which approach for which patients?

In many countries, standard therapy for mCRC has, over the past 8 years, included at least two cytotoxic agents in first line. First-line doublets have been the undisputed standard, the only debate being which doublet to choose. They have also been the platform to which newer agents – such as anti-VEGF and EGFR antibodies – have been added. However, these five studies demand that oncologists re-examine the assumptions that were made in adopting this approach. Few would deny that for some patients the use of first-line combinations may bring major advantages. However, the failure to demonstrate overall survival benefit in five large trials, involving over 4500 patients, tells us that the universal benefit of this approach has been overestimated. Indeed, if we are to maintain that groups of patients have benefited from first-line doublets, then we must also accept the possibility that others have been harmed, and may have survived longer with a sequential approach – for how else would overall survival have been so similar in the randomised trials? The challenge, therefore, is to decide the best treatment strategy for each patient.

Patients with potentially operable disease are the first group who may be expected to benefit from first-line combination therapy, and indeed there is now good evidence of long-term survivorship among patients with initially inoperable disease who have been rendered operable after the major responses sometimes seen with first-line doublets.[5] It is highly likely that patients with disease which was thought by their oncologists to be potentially 'down-stageable' will have been excluded from the trials reviewed in this article. Their data cannot therefore be used to draw any conclusions regarding this group.

Patient characteristics such as age, performance status and prior therapy might prove valuable indicators of benefit from sequential or combination strategies. Sub-group analyses in the FOCUS study examined a range of factors for interaction upon survival differences between initial combination and sequential therapy.[8] Surprisingly, no interactions were found for age, gender, prior adjuvant 5-FU therapy, the primary tumour site (colon or rectum), number of disease sites or type of disease (measurable or unmeasurable). Poor performance status (PS2) and more abnormal liver function were associated with trends towards benefit with first-line combination therapy. Although these trends did not reach significance and must be interpreted with the usual caution of sub-group analyses, they are consistent with the concept that patients with more bulky or symptomatic disease have "only one chance to respond" and are therefore more likely to benefit from the most active regimen in first line. Conversely, patients with lower-volume, less symptomatic disease may benefit from the sequential approach: single-agent therapy, if effective, will provide a bonus period of disease control; if it is ineffective, there will be sufficient time to identify this and move on to combination therapy without having lost ground.

Molecular prediction of benefit from specific cytotoxic agents may hold the key to patient selection for these different treatment strategies. In FOCUS, surplus primary tumour samples were donated by participating patients and an initial analysis has now been performed, looking

at eleven candidate predictive biomarkers for irinotecan and oxaliplatin. One of these markers, Topoisomerase-1 (Topo1), assessed using simple immunohistochemistry, has shown promise as a predictor.[12] Low Topo1 expression correlated with better outcomes for patients on FU/LV alone, but no benefit from the addition of irinotecan or oxaliplatin; moderate or high expression predicted for worse outcomes with FU/LV but increasing benefit from the addition of a second drug. These effects carried through into overall survival outcomes: patients with the highest Topo1 expression in their tumours had a major survival benefit if allocated to the initial combination treatment, while low Topo1 expressors appeared to benefit more from sequential therapy. Further investigation is now needed, including prospective clinical trials, but these findings suggest that it may in the future be possible to identify patients who will benefit from particular treatment strategies.

5. Palliation and treatment choice

If there is no major survival difference between initial combination and sequential strategies, it is particularly important to consider the issues of toxicity and quality of life.

Evidence from the five prospective studies suggests a more favourable tolerability profile with sequential therapy than with first-line combination treatment. With the exception of FOCUS2 (which used reduced-dose regimens), all of the studies reported a higher incidence of severe adverse events for combination therapy compared with single-agent therapy.[7–11] In the CAIRO study, for example, Grade 3 or 4 diarrhoea, nausea, vomiting, neutropenia and febrile neutropenia were all significantly more frequent with the capecitabine/irinotecan combination than with capecitabine alone ($p \leqslant 0.002$).[7] The FFCD study reported significantly higher incidences of haematological and non-haematological adverse events with the FOLFOX6 than with FU/LV ($p < 0.0001$).[10] In addition, more patients discontinued first-line therapy for toxicity in the combination group (16% vs. 1%, $p < 0.0001$).

The CAIRO study also evaluated the relative toxicity of the combination and sequential treatment strategies across all treatment lines.[7] The overall incidence of severe adverse events was similar in the combination (67%) and sequential (68%) groups, with only the incidence of grade 3 hand–foot skin reaction differing significantly between the groups (combination, 7%; sequential, 13%; $p = 0.004$). Although these data point to little overall difference in the toxicity profile between combination and sequential therapy across the whole treatment plan, the first-line data clearly suggest that the sequential approach can offer tolerability benefits during initial treatment.

Quality of life assessments provide another indication of the palliative effects of different treatment strategies. During the first 6 months of the FOCUS study, quality of life (assessed using the EORTC QLQ-C30 questionnaire) was similar across the treatment groups, suggesting that the greater tumour response seen with combination therapy may outweigh the effects of greater treatment toxicity.[13] In contrast, over the first 12 weeks of the FOCUS2 study, the percentage of patients experiencing improved quality of life was significantly greater for monotherapy than combination treatment ($p = 0.04$). It is possible that in the frail, elderly population taking part in that trial, even a small increase in treatment toxicity is sufficient to have a negative effect on quality of life.[9]

6. Targeted therapies

The advent of targeted therapies, such as the monoclonal antibodies bevacizumab, cetuximab and panitumumab, adds another important dimension to the management of mCRC. It also raises the question of how to interpret the conclusions of trials performed in the pre-targeted therapy era. The addition of a targeted drug to planned sequential cytotoxic therapy is an attractive but untested approach. The addition of bevacizumab to single-agent fluoropyrimidines has already been shown to be safe and effective, but is currently confined to frail patients. We must now consider the option of staged cytotoxic drugs plus targeted therapies in fitter patients. Would the conclusions of the trials reviewed in this article still apply if targeted therapies are added to cytotoxic drug sequences?

For anti-VEGF therapy, the initial striking demonstration of survival benefit came from a phase III trial in which bevacizumab was added to the relatively ineffective IFL regimen.[14] Subsequent randomised trials adding bevacizumab to more effective doublets – FOLFOX in second-line[15] and FOLFOX or CapOx first-line[16] – have shown smaller or insignificant impacts on survival. Similarly, the benefit of adding cetuximab to first-line FOLFIRI in the CRYSTAL trial[17] was modest compared with the apparent benefits seen with its addition to single-agent irinotecan in BOND.[18] The common theme is that the impact of adding targeted agents to optimum first-line doublet therapy has, to date, been no more and perhaps less striking than when the same agents were added to less effective cytotoxic platforms. We can only speculate what would have been the impact of adding bevacizumab or cetuximab to both arms of each of the trials in Table 1, but it is hard to conceive that it would have favoured the initial cytotoxic doublet approach.

7. Conclusions

Over the past decade, the increasing number of treatment options for the management of mCRC has

enabled clinicians to do more to improve outcomes for their patients. It has also presented them with the challenge of how to use these resources most effectively. The five clinical trials reviewed here provide an important data set to guide this decision.

Findings from earlier clinical studies placed first-line combination cytotoxic therapy firmly at the centre of mCRC treatment. However, these new data demand that we re-examine planned sequential therapy, starting with a single cytotoxic agent, as a treatment option for many patients, perhaps even the majority. Taken together, these studies showed no clear overall survival advantage for first-line combination therapy over pre-planned sequential therapy. Only one comparison – first-line irinotecan/FU/LV combination over sequential FU/LV then irinotecan monotherapy in the FOCUS study – showed a significant difference in overall survival, but the same study also showed that sequential FU/LV followed by combination therapy is non-inferior to first-line combination therapy.

For some patients, first-line combination therapy clearly still offers the best approach: for example, patients with potentially down-stageable metastases and, perhaps also those with bulky symptomatic disease for whom an early response is paramount. However it is also likely that other groups will benefit more from a sequential approach. It is possible that molecular markers such as Topo1 may help to identify more confidently subgroups of patients for whom one approach is superior.

What these trial data demonstrate is that first-line combination therapy is not necessarily the best approach for everyone, and that planned sequential therapy offers an effective alternative. It also offers an excellent low-toxicity platform to which targeted and other novel therapies may be added in clinical trials. The challenge moving forward is how best to match the different treatment approaches to the needs of individual patients, and to develop the strategies for identifying patients that will allow us to do this effectively.

Conflicts of interest statement

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