Chemotherapy: which drug and when?

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The treatment of advanced colorectal cancer has become very complex due to: (i) the relative efficacy of therapy, which has turned a rapidly fatal cancer into a more indolent disease in the last 10 years; (ii) the availability of four active chemotherapeutic agents and three biologics; (iii) the efficacy of several lines of therapy; (iv) the rare, but real, chance of curing stage IV patients through the combined use of chemotherapy and surgery. This article will concentrate on chemotherapy (leaving out the biologics) and will review the determinants of how aggressive the initial approach should be, the key factors of our initial treatment choices, when an intense treatment is better than just waiting or using single-agent chemotherapy; which chemotherapy is best for first, second and subsequent lines of treatment.

**Key words:** advanced colorectal cancer, doublets, single-agent chemotherapy, triplets

**introduction: identifying the goals of treatment**

The choice of which chemotherapy to choose and when to start it, depends strictly upon the goal of treatment, which in turn depends upon: (i) the clinical condition of the patient; (ii) the extent of the disease; (iii) its clinical course. Based on these factors, four main scenarios can be identified, each with specific goals and treatment choices.

The first is the condition of metastatic disease confined to the liver or lung where the hope is to radically resect the disease, rendering the patient disease free and potentially cure him. Whenever cure is not possible (the great majority of stage IV patients), three additional scenarios can be identified: patients with tumour-related symptoms who need rapid tumour shrinkage to provide palliation (second scenario); those with asymptomatic disease, but who are likely to become symptomatic in a short time period due to either bulky disease or rapid progression upon imaging (third scenario); and those with disseminated, never resectable, indolent/non-bulky disease, who are likely to remain asymptomatic for a long time period (fourth scenario). The identification of these four scenarios has two strategic consequences. The first is the recognition of the hierarchy among the clinical determinants of our choices: resectability/pursuing cure → symptom palliation → preserving tumour-related symptom-free survival as long as possible with the least toxic regimen available. The second consequence is the need to recognize when to give priority to tumour shrinkage as opposed to delaying progression. It is clear that the first two scenarios (potential respectability and presence of tumour-related symptoms) need an aggressive approach with no delay and with intense chemotherapy, whereas the third and the fourth conditions (non-aggressive, disseminated asymptomatic disease) may be best managed by a lighter treatment.

No scientific data are available on the relative frequency of the four conditions. Clinical expert opinion, though, attributes ~20% of metastatic patients to the first scenario (resectability), 20% to the second (symptoms), 30% to the third (disseminated non-symptomatic) and 30% to the fourth (disseminated indolent).

In this overview we will often refer to the four conditions, acknowledging the fact that the clinical world is much more complicated than this categorical scheme, which accounts for the reasons why we still need doctors to make clinically sound decisions and not just computers. As a dominating example, even in the fourth scenario we often end up choosing an intense treatment regimen simply due to patient preference.

**should chemotherapy always be started right away or are there conditions when waiting is non-detrimental?**

There is no question that the first and second scenarios require immediate therapy. But the third and fourth represent a challenge under this viewpoint. In fact the Nordic group demonstrated a long time ago that in asymptomatic patients, delaying the beginning of 5-fluorouracil–leucovorin (FU–LV) until the onset of symptoms resulted in shorter progression-free survival (PFS), shorter symptom-free survival and shorter overall survival (OS) compared with starting the same chemotherapy right away without waiting for symptoms [1]. But under the same experimental conditions (asymptomatic patients and using the same chemotherapy regimen), the Australasian group came to the opposite conclusion on an equivalent number of patients randomized [2]. How can the two studies be reconciled? The most plausible explanation is that the former study included a substantial number of patients who, although asymptomatic, were ‘on the verge of becoming symptomatic’ (scenario 3 type of patients), compared with a lower proportion of such patients in the latter study.
These two trials thus indicate that in order to understand how aggressive we need to be, an initial period of observation is safe only under the circumstances of patients who are likely to remain asymptomatic for a long time even with no treatment (disseminated, never-resectable, indolent/non-bulky disease, i.e. scenario 4 type of patients).

**when could single-agent fluoropyrimidine be considered the chemotherapy of choice for first-line chemotherapy?**

In general, a doublet, oxaliplatin–5-fluorouracil/leucovorin (FOLFOX) or irinotecan–5-fluorouracil/leucovorin (FOLFIRI) is superior to FU alone in terms of OS, PFS and response rate (RR) [3–6]. However, they are also more toxic. And the superiority was demonstrated mainly when treatment with the doublets after FU failure was not commercially available. When the doublets became widely available on the market, the question arose of whether the doublets used in second line after FU could provide the benefit lost when they are not used in first line. The British FOCUS and LIFE studies, the Dutch CAIRO study and the French FFCD 05 trial [7–10] provide an answer to this issue. A staged approach of single-agent fluoropyrimidine (either FU–LV or capecitabine) followed by a classical doublet chemotherapy [FOLFOX–FOLFIRI–capecitabine + oxaliplatin (XELOX)–capecitabine + irinotecan (XELIRI)] is as good as starting with the doublets in first line whenever scenario 1 and 2 patients are excluded (potentially resectable and symptomatic). These studies demonstrated superiority of the doublets over the staged approach in terms of RR and sometimes PFS, but there was no substantial loss in OS. Despite these results, the staged approach is somehow underutilized, probably because of the emphasis on RR and PFS given by oncologists and their patients.

These studies were conducted in a period when targeted therapy was not then available. However, it seems plausible that the results are also applicable to the use of chemotherapy in combination with targeted agents: the excellent results in terms of OS and PFS obtained by Kabbinavar et al. [11] using single-agent fluoropyrimidine plus bevacizumab as first-line treatment of patients who are not candidates for doublet therapy support this speculation.

**FOLFOX or FOLFIRI as first line?**

Whenever the conditions require initiation of intense chemotherapy without delay (scenario 1 and 2 patients) the choice is between FOLFOX and FOLFIRI. No matter what we choose for first line, the results in terms of OS and overall PFS (PFS of first line plus PFS of second line) is the same [12, 13]. The two studies mentioned in reference had patients with different prognoses: the former [12] had median survival in the two arms beyond 20 months, whereas the latter [13] had median survival ~5 months shorter. Despite these key differences, OS was equivalent for FOLFOX and FOLFIRI in the two studies, reinforcing the concept of equivalence between the regimens. However, it is worth emphasizing that patients failing first-line FOLFOX will have lower RR and shorter PFS when treated with FOLFIRI or irinotecan [12, 14] than do patients failing FOLFIRI and receiving FOLFOX as second-line treatment [15].

The toxicity spectra of the two doublets are different; however, the overall percentage of grade III–IV toxicity is equivalent.

**how about the triplet FOLFOXIRI?**

Two phase III studies comparing oxaliplatin–irinotecan–5-fluorouracil/leucovorin (FOLFOXIRI) and FOLFIRI have been published with conflicting results: the Italian study [16] showed superiority of the triplet in terms of OS, PFS, RR and resectability rate of liver metastases; the Greek study [17] failed to report these differences. The major difference in outcome between these studies was the median OS in the control arm (19.5 months versus 16.7 months, respectively), while the median OS in the triplet arm was comparable (21.5 months versus 22.6 months, respectively). The fact that one of these studies failed to demonstrate a survival benefit, as well as the fact that a median OS of ~21 months has been achieved in several other studies with less toxic chemotherapy do not provide support for triplet therapy with FOLFOXIRI as a general rule. FOLFOXIRI, despite its toxicity, could be considered in the occasional patient who is perfectly fit, young and with potentially resectable liver metastases.

**can capecitabine replace FU both as single agent and in combination?**

A recent meta-analysis indicated that capecitabine has similar OS and PFS to that of FU, although there is a minimal difference in RR favouring FU [18]. This single finding is not sufficient to consider capecitabine inferior to FU: significantly lower RRs were reported only in the meta-analysis, whereas that was not the case in the major randomized phase III studies comparing the two fluoropyrimidines. In addition, the favourable toxicity profile of capecitabine and the avoidance of catheter-related complications make the oral fluoropyrimidine preferable to infusional FU.

Similar considerations can be made for XELOX, where infusional FU is substituted with capecitabine in first line. Both a randomized phase III study [19] and another meta-analysis [20] in fact showed that capecitabine may safely replace 5FU in combination with oxaliplatin in first-line treatment. The same was true fox XELOX used in second line after irinotecan failure [21].

The data regarding XELIRI are not so straightforward. Two phase III studies with capecitabine plus irinotecan, EORTC40015 [22] and BICC-C [23], have shown a high incidence of severe toxicity (diarrhoea and sudden death) for this combination. However, in a phase III study with 398 patients [9] and four phase II/II studies with a total of 210 patients treated with this dose and schedule, XELIRI proved feasible and safe [24]. Possible contributing factors to
the unexpected toxicity in the EORTC and BICC-C studies may have been the use of celecoxib, which was included in the design of both studies, and regional differences in capecitabine tolerability [25]. Taken together, XELIRI may be considered as an alternative to FOLFIRI, but the dose of capecitabine should be lowered otherwise the XELIRI combination has too much gastrointestinal toxicity, as demonstrated also by a recent German trial [26].

the definition of ‘line’ of treatment with its implications

Chemotherapy cannot be continued indefinitely. After a certain period of time, chemotherapy is invariably discontinued. There are three main reasons for treatment discontinuation: tumour progression, excessive toxicity or ‘patient/doctor decision when no further tumour shrinkage is expected from continuing chemotherapy’. In the first case we can speak of failure because of ‘clinical resistance’. In the second case we speak of failure because of intolerance. But the third case is neither failure nor resistance nor intolerance: it is just ‘being tired of chemotherapy’. These differences are very important because of the implication for both clinical practice and trial design [27]. In fact any chemotherapy that will be given in the first two cases (failure) will be considered second-line treatment, whereas the third case poses a challenge. A progression occurring within 1 month of discontinuation of chemotherapy is most likely due to resistance. Thus we should consider this condition second line as well. But progression occurring after a 4-month holiday from treatment is not resistance. What do we call the line of therapy, now that we need to restart chemotherapy? Should we use the same chemotherapy that was successful at the beginning, but was stopped without clinical progression, or should we change chemotherapy to a different regimen? This condition is not second line. It is still first line. The choice of chemotherapy will depend upon: (i) the extent of benefit of the true first line: the more benefit, the stronger the indication for a ‘rechallenge’ with the same chemotherapy; (ii) the length of the holiday: the longer, the stronger the indication for rechallenge.

All these concepts are very relevant as well when we desperately look for a therapeutic option in the heavily pretreated patient. In fact we should always make certain that the patient has indeed failed all previous lines of therapy, otherwise, ‘rechallenge’ is the best option.

any role for single-agent oxaliplatin?

No. The second-line registration trial of FOLFOX versus oxaliplatin versus FU–LV in patients failing irinotecan-based therapy demonstrated only 1% RR and inferior OS for oxaliplatin alone as compared with FOLFOX [28]. FOLFOX in that setting gave 10% RR and produced an advantage in OS as compared with the other two arms of the trial. For this reason, oxaliplatin needs to be combined always with a fluoropyrimidine (or another agent) for efficacy. This contrasts with irinotecan, which is active in this disease even as a single agent.

irinotecan alone or FOLFIRI as second line after oxaliplatin failure?

In general both irinotecan alone and FOLFIRI can be considered standard second-line regimens after oxaliplatin failure. One would be tempted to think that FU could be spared in second line after failing first line (as a component of FOLFOX or XELOX chemotherapy). However, the FOCUS British study, which included an arm with irinotecan alone and another arm with FOLFIRI, indicated that the doublet had slightly better efficacy than irinotecan alone and was more tolerable [7]. Therefore the doublet is generally preferred in the second-line setting.

any role for IROX?

Haller et al. [29] randomized 628 patient with advanced colorectal cancer who failed first-line single-agent fluoropyrimidine, to receive either irinotecan alone or irinotecan–oxaliplatin (IROX). There was a statistically significant difference in OS for the experimental arm: median OS 13.4 versus 11.1 months, hazard ratio (HR) 0.78. All secondary endpoints significantly favored IROX with an almost doubling of the median PFS improvement of tumour-related symptoms and a tripling of the RR. Compared with irinotecan, IROX produced more grade 3–4 diarrhoea (28% versus 23%) and severe neuropathy. Does this mean that IROX is the best doublet as second-line treatment of patients failing FU? We have an indirect answer to this question from trial 9741 [5] [first-line FOLFOX versus IROX versus irinotecan and bolus 5-fluorouracil–leucovorin (IFL)]; this study showed that IROX was inferior to and more toxic than FOLFOX in the first-line setting. Therefore IROX is not the most efficacious second-line treatment, since it is possible that FOLFOX or FOLFIRI are equally effective after first-line fluoropyrimidine failure. IROX, therefore, does not change, but enriches the treatment algorithm of advanced colorectal cancer at the second-line level [30]. In general, IROX is to be preferred whenever patients are intolerant to FU or possibly when the clinical situation indicates that second-line treatment will be the last antineoplastic treatment for these patients.

disclosures

Alberto Sobrero has served on the advisory boards of AstraZeneca, Roche, Sanofi Aventis, Merck Serono, Bayer, Onyx, Amgen and has spoken at satellite symposia of Roche, Sanofi Aventis, and Merck Serono

references


