Chemotherapy, which drugs and when

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Introduction

The median overall survival (OS) of patients with metastatic colorectal cancer (mCRC) is significantly increased by the use of chemotherapy. Although new targeted agents such as antibodies to the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) have provided additional benefit to mCRC patients, chemotherapy remains the backbone of treatment. The available cytotoxic drugs with proven efficacy are the fluoropyrimidines [5-fluorouracil (5-FU), capecitabine, uracil/tegafur (UFT/LV)], irinotecan, and oxaliplatin. In this review we will summarise the most relevant data concerning the efficacy of each of these drugs, their use in combination chemotherapy, their sequential versus combined use as well as their preferred sequence, the optimal time to initiate treatment, the optimal duration of treatment, its use as neo-adjuvant treatment in patients with potentially resectable metastases, and the current status of predictive markers for outcome.

Fluoropyrimidines

For many decades, 5-FU with or without leucovorin (LV) was the only available treatment for patients with mCRC, which resulted in a median overall survival of approximately 11–12 months [1]. Despite many efforts, no outright preference for a particular dose or schedule has been identified [2]. The main toxicities for bolus schedules are diarrhoea, stomatitis, and neutropenia, and infusional schedules result in less haematological toxicity but more hand-foot syndrome. More recently, oral fluoropyrimidines have become available, of which capecitabine and UFT have been tested in mCRC. Both oral agents have shown comparable results in overall and progression-free survival but an improved tolerability to bolus 5FU/LV [3–8]. In comparison to bolus 5FU/LV, capecitabine has a lower incidence rate of stomatitis, diarrhoea, nausea, alopecia, neutropenic fever, and treatment-related hospitalisation rate, and a higher incidence of hand-foot syndrome and uncomplicated hyperbilirubinaemia. UFT/LV when compared with 5FU/LV is associated with less stomatitis, diarrhoea, nausea/vomiting, neutropenia, and documented infection. Uncomplicated hyperbilirubinaemia is observed with UFT/LV as well.

Irinotecan

Irinotecan is a topo-isomerase I inhibitor, and its main toxicities are nausea/vomiting, diarrhoea, alopecia, myelosuppression, and a cholinergic syndrome. It first showed efficacy as second-line treatment in 5-FU-refractory mCRC patients [9,10]. The obvious next step was to investigate its use in first-line combinations with 5-FU/LV. Two studies with irinotecan plus either bolus or infusional 5-FU/LV compared to 5-FU/LV alone showed a significant absolute benefit in median overall survival of 2.2 and 3.3 months, respectively [11,12]. However these studies have been criticised for the fact that effective second-line treatment with irinotecan in the control arm was not a prospective part of the study design [13].

Oxaliplatin

Oxaliplatin is an alkylating agent of the platinum family, and its main toxicities are a (often reversible) sensory neuropathy, nausea/vomiting, diarrhoea, and myelosuppression. Given its synergistic activity with fluoropyrimidines [14] it is usually administered in combination with a fluoropyrimidine. This combination has efficacy as a second-line treatment after failure on 5-FU and irinotecan [15]. Initial studies in which the addition of oxaliplatin to 5-FU/LV was compared to 5-FU/LV alone in first-line treatment did show a benefit in response rate and progression-free survival for the combination, but not in overall survival [16,17]. However, these studies were not designed to demonstrate a benefit in overall survival, despite the fact that certainly at that time this

endpoint was considered to be the gold standard. In 2004, a combination of infusional 5-FU/LV and oxaliplatin (FOLFOX) was shown to significantly prolong the median overall survival compared with a bolus 5-FU/LV/irinotecan regimen (IFL) [18]. In many countries these results have shifted the preference to FOLFOX as first-line regimen. However, as with studies on first-line irinotecan-based combination treatment, second-line treatment was not a prospective part of the study design. In this study there was an imbalance in the use of salvage treatment, since 60% of patients received second-line irinotecan after failure on FOLFOX, but, due to its limited availability at the time this study was conducted, only 24% of patients failing IFL received oxaliplatin. The finding that the absolute difference in median overall survival (4.5 months) was greater compared to the difference in median time to progression (1.8 months) also suggests that salvage treatment had a significant impact on survival outcome [13]. Furthermore, the different modes of 5-FU administration between the two treatment arms (continuous versus bolus infusion) may have been responsible for the higher incidence of severe toxicities as well as the decreased efficacy in the IFL arm. This latter view is supported by the results of another randomised study in which FOLFOX and infusional 5-FU/LV plus irinotecan (FOLFIRI) had comparable overall survival results, although it should be noted that overall survival was not the primary endpoint of this study [19]. Therefore, despite the fact that combination treatment of 5-FU with either irinotecan or oxaliplatin was widely accepted as the new standard in the first-line treatment of mCRC, the question whether its benefit would have been maintained if patients would have received appropriate salvage treatment in the control arm of these studies was left unanswered. The validity of this question first came from a retrospective analysis that showed a correlation between survival and the number of effective drugs to which patients had been exposed [20]. In other words, it may be more important that patients are exposed to these drugs during the course of their disease, rather than receiving these drugs in first-line.

Sequential or combination treatment

Two important studies with a novel design have provided a better insight in this issue. The only study that prospectively evaluated the sequential versus concomitant use of all three effective cytotoxic drugs, i.e. a fluoropyrimidine, irinotecan and oxaliplatin, is the CAIRO study of the Dutch Colorectal Cancer Group (DCCG) [21,22]. In this study the treatment with first-line capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin was compared with first-line capecitabine plus irinotecan, and second-line capecitabine plus oxaliplatin. Upfront combination treatment did not result in a significant overall survival benefit compared to sequential treatment. The FOCUS study of the Medical Research Council (MRC) UK confirmed this finding [23]. In this study the sequential versus concomitant use of either irinotecan or oxaliplatin with infusional 5-FU/LV was tested in separate treatment arms, and no advantage was demonstrated for combination therapy. Therefore, the CAIRO and FOCUS studies demonstrate that the sequential use of cytotoxic agents remains a valid treatment option in mCRC patients. The results of CAIRO and FOCUS have been questioned [24], however, with invalid arguments since both studies do not argue contrary to previous study results, but were unique in their design [25,26]. Combination treatment may be preferred to the sequential use of the same drugs in two groups of patients. First, in patients for whom tumour shrinkage is the primary objective (i.e. for palliation of local symptoms or a possible resection of metastases after down-sizing), since combination treatment results in a higher response rate compared to fluoropyrimidine monotherapy. Second, combination treatment may be preferred in patients with a decreased performance status. These patients are at risk that their medical condition may not allow any salvage treatment after progression on first-line, and therefore have less chance to be exposed to all effective drugs during the course of their disease, which has shown to be of benefit in the general study population [20]. Obviously, the higher response rate has to be balanced against the increased toxicity in each individual patient. Since a large group of patients present with relatively few symptoms and/or will not become eligible for resection of metastases, CAIRO and FOCUS have taught us that the sequential use of cytotoxic drugs starting with fluoropyrimidine monotherapy is a valid treatment option for the majority of mCRC patients. (25) Both studies were conducted in a period when targeted therapy was not yet available. However, it seems plausible that the results are also applicable to the use of chemotherapy in combination with targeted agents. Recently, the combination of irinotecan + oxaliplatin (IROX) showed a significant benefit in progression-free and overall survival compared to irinotecan monotherapy after failure on fluoropyrimidine monotherapy [27]. Therefore, whenever a patient does not need aggressive treatment, a staged

approach of fluoropyrimidine plus bevacizumab may be followed by either IROX or a fluoropyrimidine plus oxaliplatin or irinotecan (with the other of these two latter drugs being administered in third line). The choice between these options may be based upon the toxicity profile of a specific regimen, with a possible preference for IROX in situations where third-line therapy appears not feasible. In patients who are intolerant to fluoropyrimidines, IROX appears to be a good alternative.

5-FU, irinotecan, and oxaliplatin (FOLFOXIRI)

Two phase III studies on a comparison between a combination of 5-FU/LV plus irinotecan plus oxaliplatin (FOLFOXIRI) and FOLFIRI have been published [28,29], with conflicting results. The major difference in outcome between these studies was the result on median overall survival in the control arm (16.7 months versus 19.5 months, respectively), while the median overall survival in the triplet arm was comparable (22.6 months versus 21.5 months, respectively). The only difference in the scheduling of drugs between the two studies was the timing of 5-FU/LV administration in relation to irinotecan and oxaliplatin. A disadvantage of the triplet combination may be that, when compared to doublet combinations, the combined use of three drugs will limit their dose-intensity. The fact that one of these studies failed to demonstrate a survival benefit, as well as the fact that median overall survival times of around 21 months have been achieved in several other studies with doublet therapy, do not provide an outright support for triplet therapy with FOLFOXIRI. The increased incidence of toxicity by triplet therapy may also hamper its use in combination with targeted agents. Lastly, the much higher response rate of 58% and median time to progression of 13 months that was observed with FOLFOXIRI in a phase II trial [30] compared to the phase III results obtained by the same group (43% and 8.4 months, respectively) again underscores the importance of large prospective randomised trials to assess the value of novel treatment strategies in the general population.

Irinotecan or oxaliplatin?

Several studies have compared the use of irinotecan versus oxaliplatin in combination with 5-FU/LV in first-line treatment. The small percentage of patients that experience severe toxicity by irinotecan is more likely to be hospitalised, while a larger percentage of patients experience dose-limiting toxicity by oxaliplatin but in most cases remain outpatients. In a well-designed randomised study of FOLFOX versus FOLFIRI with a planned cross-over upon progression [19], the incidence of serious adverse events was higher in patients treated with FOLFIRI (14% versus 5%), but the overall incidence of grade 3–4 toxicities as well as the percentage of patients that had to discontinue treatment for reasons of toxicity was greater upon treatment with FOLFOX (74% versus 53%, and 11% versus 6%, respectively). This study did not demonstrate any significant difference in median progression-free or median overall survival or first-line response rate. Based on the results from this and other comparative studies it can be concluded that there is no preference for irinotecan or oxaliplatin in the first-line treatment in terms of efficacy, and that the choice can be made on individual patient preferences [31].

Capecitabine replacing 5-FU in combination schedules

Given the results of trials comparing capecitabine with 5-FU, it was logical to test whether 5-FU could be replaced by capecitabine in combination schedules. A recent meta-analysis showed that capecitabine may safely replace 5-FU in combination with oxaliplatin (CAPOX) [32]. Two phase III studies with capecitabine plus irinotecan (CAPIRI), EORTC-40015 and BICC-C, have shown a high incidence of severe toxicity (diarrhoea and sudden deaths) for this combination in 44 and 145 treated patients, respectively [33,34]. However, in a phase III study with 398 patients [22] and four phase I–II studies with a total of 210 patients treated with this dose and schedule, CAPIRI proved feasible and safe [35]. 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 [36]. Taken together, CAPIRI may be considered as an alternative to FOLFIRI [35], and dose reductions should be considered in patients at risk for severe toxicity, as with any schedule.

When to start?

Few data are available on the issue of the optimal time to initiate palliative systemic treatment, and these were performed in a period in which 5-FU/LV was the only treatment available and in which screening methods were less advanced. On top of this, the two studies

that addressed this topic provided contradictory results [37,38]. Given the increased benefit of palliative systemic treatments over the years, it seems justified to initiate treatment in asymptomatic patients. However, watchful waiting may also be an option in selected cases with low tumour burden.

Optimal duration of treatment

A MRC study randomised patients with stable disease or better after 12 weeks of treatment between continuous treatment until progression or discontinuation of treatment with resumption of the initial treatment at progression. It was concluded that a discontinuation of treatment did not result in a decreased overall survival [39]. However, since many eligible patients refused to be randomised, and patients randomised to observation did not always receive the scheduled treatment at progression, the final results are difficult to interpret. The results of the OPTIMOX2 trial suggest a benefit of continuous versus discontinuous treatment; [40] however, this trial was underpowered due to its premature discontinuation resulting from the introduction of bevacizumab. Currently, no firm recommendation can be made on the optimal duration of treatment with chemotherapy. If treatment is well tolerated, it seems justified to continue until disease progression. However, a treatment holiday may be proposed to patients with no change in disease status at subsequent evaluations, and certainly if they wish so. Most patients receiving oxaliplatin will develop invalidating neurotoxicity at some time during treatment. The OPTIMOX study has shown that after six cycles of FOLFOX, oxaliplatin may be safely stopped while continuing 5-FU/LV for a further 12 cycles after which oxaliplatin is reintroduced again, without compromising efficacy [41]. Trials on the optimal duration of chemotherapy plus targeted agents are ongoing, such as the French OPTIMOX3 study (capecitabine or 5-FU with oxaliplatin plus bevacizumab followed by bevacizumab and erlotinib), and the CAIRO3 study of the DCCG (CAPOX and bevacizumab followed by randomisation between capecitabine plus bevacizumab or observation until progression, after which the initial 3-drug induction treatment is resumed) [42].

Use of neo-adjuvant chemotherapy in unresectable metastases

Data from neo-adjuvant chemotherapy aiming at the down-sizing of initial unresectable metastases in order to allow secondary resections are derived from retrospective uncontrolled series. Given the low feasibility of randomisation between surgery and no surgery this cannot be tested in a prospective randomised trial. Although promising results of long-term survival for this approach have been presented [43], survival data from patients with comparable baseline characteristics treated with up-to-date systemic treatment are not available. This implies that we do not even have data from appropriate historical controls to assess the value of secondary surgery. Although a benefit from secondary resections seems likely, the clinical relevance of this benefit remains uncertain [13]. Residual vital tumour cells were shown to be present in the great majority of metastatic lesions that went into complete remission by chemotherapy [44]. This argues against this strategy in patients that become resectable by a reduction in number rather than in size of metastases. In neo-adjuvant chemotherapy schedules there is by far the most expertise with oxaliplatin. Since oxaliplatin is associated with less severe hepatotoxicity compared with irinotecan, there may be a preference for oxaliplatin in this setting [45]. Given the correlation between the duration of chemotherapy and the morbidity of liver surgery, it is recommended to limit the number of neo-adjuvant cycles.

Predictive markers for chemotherapy

Even with the increased efficacy of chemotherapy, many patients still do not respond to chemotherapy. Therefore, there is a need for predictive markers that allow the selection of patients that are most likely to benefit from treatment as well as to prevent unnecessary toxicity in non-responding patients. Most studies on this topic concerned biomarkers in relation to response to fluoropyrimidines, such as dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), and thymidylate synthase (TS). In the adjuvant setting it has been shown that patients with a deficient mismatch repair (dMMR) system do not benefit from fluoropyrimidine treatment. However, the incidence of dMMR in mCRC patients is very low and therefore of no practical consequence [46]. Examples of predictive markers for oxaliplatin and irinotecan are excision cross-complementing gene (ERCC1), and topo-isomerase-1 (Topo1). Although positive results for some of these markers have been presented, these were not confirmed by others [47–54]. Major problems of these studies are that they were retrospective of nature, and obviously limited to patients of whom tumour material was available. As

to the latter, this almost invariably concerned tissue of the primary tumour, and for many markers it is yet unknown whether test results from primary tumours are representative for metastatic tissue. To date, no marker that predicts the response to chemotherapy is considered to be useful in routine clinical practice yet [55,56]. This probably reflects the fact that these markers are not as specific as, for instance, the KRAS mutation status in epidermal growth factor receptor-directed therapy. Further retrospective studies are therefore unlikely to increase our knowledge in this field [57]. Despite the complexity of their design which hampers their feasibility, this insight can only be expected from prospective randomised studies.

Conclusions

Chemotherapy remains the backbone of treatment of patients with mCRC. With the use of fluoropyrimidines, irinotecan and oxaliplatin, the percentage of patients that achieve long-term survival has increased to approximately 10% [58]. It is expected that this will be further increased with the use of targeted agents. Patients in whom tumour shrinkage is the primary goal or who are less likely to be eligible for salvage treatment are good candidates for upfront combination regimens. The remaining majority of patients also have the option of receiving sequential treatment starting with fluoropyrimidine monotherapy. Capecitabine is a good alternative for 5-FU, both when given as monotherapy and in combination schedules. The choice between irinotecan and oxaliplatin may be made on individual preferences. No outright recommendations can be made on the optimal time to initiate chemotherapy or the optimal duration of treatment. Studies on currently known biomarkers have not provided useful results for clinical practice in that the response to chemotherapy may be predicted. The prognosis of mCRC patients will undoubtedly be further improved in the near future by a more optimal incorporation of currently available targeted drugs in treatment schedules as well as the development of new (targeted) drugs and biomarkers. Multidisciplinary teams consisting of surgeons, medical oncologists, radiotherapists, radiologists, and pathologists should establish the best available treatment for each individual patient.

Conflict of interest statement

None declared.

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