Re-challenge and the concept of lines of therapy in metastatic colorectal cancer

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Introduction

Colorectal cancer is the third most frequently diagnosed cancer, and the fourth leading cause of cancer death in the world [1]. Colon cancer incidence is rising in some parts of the world, especially in Asia. Mortality from colon cancer has decreased over the past 30 years, partly due to better treatment modalities.

Approximately 40% of patients diagnosed with colorectal cancer will develop colorectal metastases. In our experience two thirds of these patients have synchronous metastases. Most of the remaining third, who have metachronous metastases, will have received adjuvant therapy based on fluoropyrimidine with or without oxaliplatin. As patients previously exposed to these drugs may still have sensitive tumours, this can influence the management of these patients.

The prognosis of patients with metastatic colorectal cancer (MCRC) has been improving in recent years, from a median survival of 12 months or less when 5-fluorouracil was the only available drug to more than 2 years with new drugs and optimal management. In addition to fluoropyrimidines, oxaliplatin and irinotecan are the cornerstones of chemotherapy, while bevacizumab, a monoclonal antibody targeting angiogenesis, and cetuximab or panitumumab, both monoclonal antibodies targeting EGFR, are now available in many countries. Several other factors may also explain the prolonged survival: careful follow-up of patients after curative surgery of the primary cancer, allowing an earlier diagnostic of metastases; increasing use of chemotherapy in the growing elderly population – median age of patients with colon cancer is above 71 years; and surgery of metastases, even in those patients with initially unresectable metastases, when chemotherapy induces a notable tumour shrinkage [2,3].

Two essential parts of the global management of MCRC will be discussed in this paper: the concept of lines of therapy and the re-challenge of a previously administered treatment.

Due to the availability of several drugs, multiple regimens have been developed in the treatment of MCRC. These regimens are more active than fluoropyrimidines alone and have no cross-resistance, meaning that patients whose tumours have become resistant to the initial regimen may still be sensitive to another regimen. The concept of lines of therapy is defining the best sequence using different regimens and also the most efficient approach between an "aggressive strategy" using more than two drugs front-line – thus limiting the number of possible lines – and a "conservative strategy" allowing administration of more therapeutic lines. The goal of the aggressive strategy is to increase as much as possible the initial duration of disease control and the response rate, to improve the metastasis resection rate, while the goal of the conservative strategy is to control the tumour growth with safer regimens. The potential drawbacks of the aggressive strategy are more toxicity and a limitation of the rescue options when the tumour has become resistant; those of the conservative strategy are less possible surgical rescue and potentially less patients able to receive all available drugs as tumour progression and comorbidities may not allow the administration of a drug at a late stage.

Re-challenge or reintroduction of a previously administered treatment is also a growing part of the management of MCRC. This new approach is driven by two different reasons. The first one is the cumulative toxicity of drugs like oxaliplatin. Most patients are forced to stop oxaliplatin, not for acquired tumour resistance, but for a cumulative neurosensory toxicity. Thus the full potential of oxaliplatin-based therapy is not achieved if patients are treated until neurotoxicity. While this neuropathy is at least partially reversible, the time needed, usually more than 6 months, is not compatible with reintroduction in most patients as second-line therapy does not control the tumour

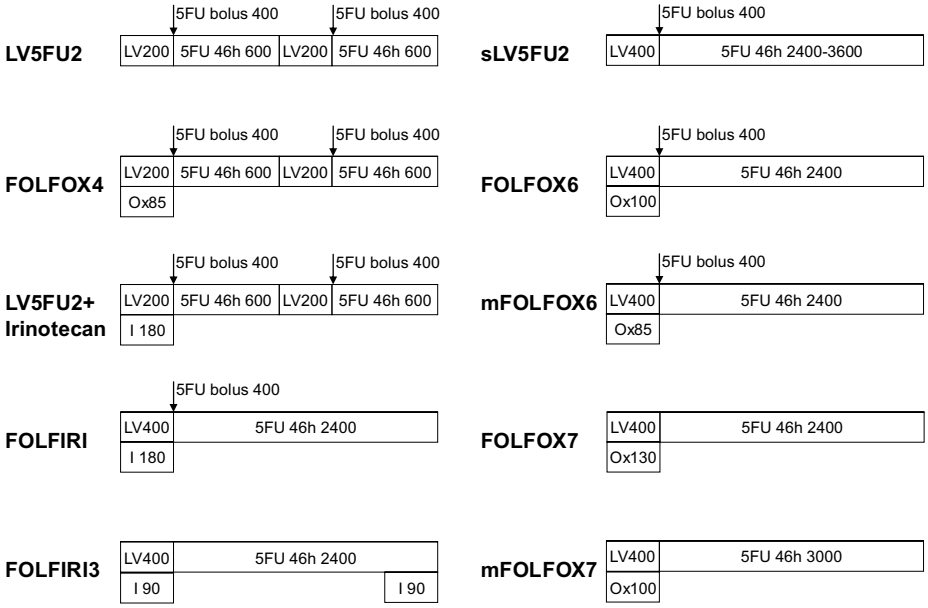

Fig. 1. Bimonthly regimens. LV: leucovorin, 5FU: 5-fluorouracil, Ox: oxaliplatin, I: irinotecan, s: simplified, m: modified.

for such duration in a majority of patients. This has led to the concept of oxaliplatin reintroduction or stop and go: giving oxaliplatin-based therapy for a limited number of cycles to avoid a severe neuropathy, stopping the drug and reintroducing it later after either a fixed interval or at tumour progression. The second reason for rechallenging is the prolonged survival now achieved in MCRC. Continuous chemotherapy for years has side effects and impacts on the patient's ability to receive new therapy. It also renders the tumour multi-resistant. These facts were the basis for exploring stopping chemotherapy in responding patients. A similar approach is well recognised and used in other cancers like ovarian cancer where patients are managed according to the concept of platinum sensitivity. Patients having a platinum-free interval of more than 6 months after a tumour response are considered platinum-sensitive while those with a shorter platinum-free interval are considered platinum-resistant.

The present paper is divided into four sections, dealing with lines of therapy, oxaliplatin stop and go, stopping chemotherapy or chemotherapy-free intervals (CFI), and the role of targeted therapies during the maintenance phase or the chemotherapy-free interval.

I. The concept of lines of therapy

First-line therapy regimens

The different regimens used in first-line therapy have a chemotherapy backbone. This can be fluoropyrimidine alone, 5-fluorouracil or capecitabine; doublets with fluoropyrimidine and oxaliplatin or irinotecan, either FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) or XELOX (capecitabine, oxaliplatin) or FOLFIRI (folinic acid, 5-fluorouracil, irinotecan); triplets with fluoropyrimidine–oxaliplatin–irinotecan (FOLFIRINOX). All regulatory-approved regimens are listed in therapeutic guidelines.

Targeted therapies can be added to most chemotherapy regimens. The regimens that have shown a benefit over chemotherapy alone are: bevacizumab with fluoropyrimidine alone, with fluoropyrimidine plus irinotecan, or with FOLFOX or XELOX (capecitabine, oxaliplatin); cetuximab with FOLFIRI and panitumumab with FOLFOX, both in *KRAS* wild-type tumour.

It is outside the scope of this paper to review and discuss all these regimens. Figure 1 shows the bimonthly regimens described in this paper.

Combination or sequential therapy

Should we use fluoropyrimidine monotherapy, doublets or triplets in first-line? Registration studies have shown that combination therapies were more active than fluoropyrimidines alone in terms of response rate (RR), progression-free survival (PFS) and even, in some trials, overall survival [4–6].

Three studies addressed the question of monotherapy versus combination therapy. The CAIRO 1 study randomised 820 patients [7]. The first arm was sequential therapy: capecitabine first-line, followed by

irinotecan second-line, followed by XELOX third-line; the second arm was combination therapy: XELIRI (capecitabine, irinotecan) followed by XELOX. The FOCUS trial involved 2135 patients randomised to five different arms: modified LV5FU2 (leucovorin, 5-fluorouracil) followed by irinotecan (arm 1) or FOLFIRI (arm 2) or mFOLFOX6 (arm 3), FOLFIRI (arm 4) and mFOLFOX6 (arm 5) [8]. Both trials failed to show a survival advantage for the front-line combination. However, both trials achieved poor median survivals compared to pivotal trials with the same regimens, 17.4 months for the combination vs. 16.3 months for sequential therapy in the CAIRO 1 trial, 15.4 and 16.7 months for the combinations (arms 4 and 5) vs. 15.0 and 15.2 for monotherapy followed by combinations (arms 2 and 3) vs. 13.9 for sequential monotherapy (arm 1) in the FOCUS trial. Two pitfalls explaining the low survival were common to the two trials: salvage surgery was not performed and a low proportion of patients (19–55% according to arms) received the three active drugs, fluoropyrimidines, oxaliplatin and irinotecan. A third study conducted in 410 patients in France showed similar results [9].

The advantage of monotherapy is a lower toxicity. However, if combinations are administered later during the course of the disease, toxicity could be worse with the same regimen in second-line than in first-line therapy. Of note, patients with poor prognosis are most likely unable to benefit from monotherapy. Fluoropyrimidines alone could be an option in patients with non-operable sites without adverse prognostic factor. However, in our experience, only 18% of patients belong to this sub-group (baseline performance status 0 and normal LDH, no surgery of metastase). Based on these data, as soon as we are unable to predict the sensitivity to fluoropyrimidines alone, we believe that only patients unable to receive a combination, refusing intravenous chemotherapy or having a low-risk inoperable MCRC can receive front-line monotherapy. On the other hand, starting with combination therapy followed by maintenance therapy, as discussed below, may have the same safety advantage as starting with monotherapy followed by combination therapy plus the potential benefit of reintroducing the initial combination regimen at progression.

Second- and third-line therapy

Most patients should be offered second-line therapy when tumour progression or unacceptable toxicity close the first-line therapy. The choice of the first-line therapy imposes the second-line treatment. The knowledge of the most active second-line regimens must not lead to using a suboptimal first-line regimen.

It has been reported that exposure to all available agents could be more important than the number of lines [10]. However, based on the correlation between the percentage of patients who received all the available drugs and the median survival, if all eligible patients receive all the drugs, the median survival would still be limited to 22 months. New strategies using targeted agents or the oxaliplatin stop-and-go strategy have already achieved median survival well over 22 months and argue against this basic approach.

Effective second-line therapies are available. Classical doublets are active after failure of LV/5FU or capecitabine. FOLFOX remains active after FOLFIRI, but irinotecan or FOLFIRI appear less active after FOLFOX [3]. New irinotecan-based chemotherapy regimens such as FOLFIRI3, based on a positive interaction between irinotecan given after 5FU infusion, could be more active than FOLFIRI in second-line therapy, but they have not been evaluated in randomised trials [11–13].

Targeted therapies have also improved second-line therapy. Bevacizumab with FOLFOX4 after 5FU/irinotecan failure has improved response rate, PFS and overall survival [14]. Continuing bevacizumab after progression on first-line therapy may also prolong survival and is being evaluated in prospective trials [15]. Vatalanib, a VEGFR tyrosine kinase inhibitor, with FOLFOX after 5FU/irinotecan failure has demonstrated prolongation of PFS [16]. Cetuximab with irinotecan after 5FU/oxaliplatin failure has shown prolongation of PFS compared to chemotherapy alone even though the results in the small subset of patients tested for *KRAS* were not convincing [17,18]. Panitumumab plus FOLFIRI also prolonged the median PFS of approximately 2 months [19]. However the magnitude of the PFS benefit remains modest and consistently below 3 months and a benefit in OS was observed only in the bevacizumab trial [14]. One acceptable hypothesis to explain the discrepancy between PFS and OS is cross-over in the chemotherapy-alone arms.

After two lines of treatment, a significant number of patients are still able and willing to receive therapy. The BOND trial, in which a significant proportion of patients were not only refractory to irinotecan-based chemotherapy but also to oxaliplatin-based chemotherapy, has demonstrated a synergy between irinotecan and cetuximab. The response rate for irinotecan plus cetuximab was superior to the response rate of the

monoclonal antibody alone [20]. Later, it was demonstrated that the anti-EGFR monoclonal antibodies cetuximab and panitumumab were also active alone in third-line versus best supportive care, results amplified in the wild-type *KRAS* population [21,22]. Of note, bevacizumab is not active in third-line therapy [23].

An important practical question for the majority of patients who have a non-resectable tumour, even in case of tumour shrinkage, is when to use cetuximab or panitumumab? There are limited data and no prospective trial to answer this important question. As the only active third-line therapies are based on anti-EGFR monoclonal antibodies, which are only active in wild-type *KRAS* tumours, there is no third-line therapy for patients with mutated *KRAS* tumours and for patients with wild-type *KRAS* tumours who received anti-EGFR treatment in first- or second-line therapy. While there is an unquestionable survival advantage for anti-EGFR monoclonal antibodies in third-line therapy, there was no survival advantage in second-line therapy in the EPIC trial, although that can be due to cross-over: half of the control patients received cetuximab in third-line therapy [17]. There is also no survival advantage in first-line therapy in the COIN trial evaluating cetuximab with FOLFOX or XELOX and in the PRIME trial evaluating panitumumab with FOLFOX [24,25]. The only significant improvement in overall survival (median increased by 3.5 months) in a first-line trial has been reported in the CRYSTAL trial [26]. Unfortunately, the positive results came from a retrospective analysis and the proportion of patients having received cetuximab after the first-line in the control arm has not been reported. A limited number of cross-over patients (cetuximab in second or third line) in the control arm may explain this survival advantage for cetuximab in first-line therapy. Based on these data, it is too early to recommend the systematic use of anti-EGFR antibody in first-line therapy in patients with wild-type *KRAS* unresectable metastases, especially in combination with oxaliplatin.

Oxaliplatin-based or irinotecan-based regimen?

The choice between oxaliplatin-based and irinotecan-based regimens is a matter of debate. Tournigand and colleagues randomised metastatic colorectal cancer patients to irinotecan or oxaliplatin, both given in combination with a simplified LV5FU2 infusion [3]. This was the first trial that directly compared the addition of oxaliplatin or irinotecan in combination with infusional 5-FU and leucovorin. Final results did not show any difference between FOLFIRI and FOLFOX6 in first-line therapy in terms of response rates and PFS. The FOLFIRI regimen was less active in second-line therapy in patients failing FOLFOX6 than FOLFOX6 after progression on FOLFIRI. Of note, more than 70% of the patients did receive the second-line therapy and 13% of the patients had R0 surgery of metastases on FOLFOX, 7% on FOLFIRI. Median overall survival for both regimens was over 20 months. These results support the concept that treatment with sequential regimens optimises outcome for patients.

The fluoropyrimidine regimen can also influence the choice between the doublet regimens, especially in combination with irinotecan: IFL (irinotecan with 5FU bolus) was proven less active and more toxic than FOLFOX [27,28]. FOLFIRI as performed in the Tournigand study could be more active than irinotecan with the standard LV5FU2 or IFL or XELIRI [5,6,29]. However, from the Tournigand study [3], arguments favouring FOLFIRI first-line were less grade 3–4 toxicity and better activity of FOLFOX second-line (response rate 15% vs 4%, PFS second-line 4.9 vs. 2.3 months) while arguments in favour of FOLFOX first-line were less patients with serious adverse events and more patients amenable to surgery of metastases. However, the difference in the incidence of grade 3–4 toxicity is due to grade 3 neutropenia, which is in most cases not clinically relevant, and the study was not designed or powered to evaluate salvage surgery. Another result of this study favoured FOLFOX: to achieve the same results, patients in the FOLFOX6 arm received 44.5% less cycles of combination chemotherapy (1081 cycles) than patients in the FOLFIRI arm (1562 cycles). This is explained by the cumulative oxaliplatin-based neurosensory toxicity: most patients stopped oxaliplatin for neurotoxicity and not for tumour progression. If neurotoxicity could be managed or FOLFOX reintroduced after recovery from neurotoxicity, then the potential of FOLFOX could be improved.

Finally, if this argumentation is correct, the most active doublets appear to be the cornerstone of chemotherapy.

II. Oxaliplatin stop-and-go strategy

One potential approach to optimise the use of oxaliplatin and avoid the problem of oxaliplatin neurotoxicity is to administer the FOLFOX regimen for a defined period of time, stop therapy before severe neurotoxicity develops, and later reintroduce the regimen. This approach is supported by the observation that oxaliplatin reintroduction was clinically effective in a series of patients who stopped

oxaliplatin for neurotoxicity and recovered before reintroduction [30].

The oxaliplatin stop-and-go strategy was evaluated in the OPTIMOX1 trial [31]. Patients with metastatic colorectal cancer were randomised to either FOLFOX4 until progression or the OPTIMOX1 strategy, which consisted in 6 cycles of FOLFOX7 [32] followed after an assessment for possible salvage surgery by maintenance therapy with the simplified LV5FU2 regimen without oxaliplatin. After 12 cycles of LV5FU2 chemotherapy, FOLFOX7 was reintroduced in patients with stable disease or response. Six hundred and twenty patients were enrolled, including an exploratory cohort of 95 elderly or poor prognosis patients. Median progression-free survival and survival times were 9.0 and 19.3 months, respectively, in patients allocated to FOLFOX4 compared with 8.7 and 21.2 months, respectively, in patients allocated FOLFOX7/sLV5FU2. Differences were not statistically different. Fewer patients experienced grade 3 or 4 toxicity in the investigational arm. Including oxaliplatin reintroduction, grade 3 sensory neuropathy was observed in 17.9% of patients allocated FOLFOX4 and 13.3% of patients allocated FOLFOX7/sLV5FU2. In the investigational arm, oxaliplatin was reintroduced in 40% of the patients and achieved response or stabilisation in 69.4% of these patients. The OPTIMOX1 study demonstrated that a short induction with oxaliplatin followed by maintenance therapy was better tolerated, while achieving similar efficacy, than continuous administration of the drug until progression or the occurrence of the cumulative neurotoxicity.

The OPTIMOX1 study has also suggested that oxaliplatin reintroduction was associated with improved survival in advanced colorectal cancer [33]. The impact of oxaliplatin reintroduction on OS was potentially masked by the fact that a large number of patients did not receive the planned oxaliplatin reintroduction or received oxaliplatin after second-line therapy in both treatment groups. A Cox model fitted with all significant baseline factors plus time-dependent variables reflecting tumour progression, reintroduction of oxaliplatin, and use of second-line irinotecan, demonstrated that oxaliplatin reintroduction had an independent and significant impact on OS (HR = 0.56, $P = 0.009$). It was also shown that the percentage of patients with oxaliplatin reintroduction had a significant impact on OS. Centres in which more than 40% of the patients were reintroduced had an adjusted HR for OS of 0.59 compared with centres in which no patient was reintroduced.

The Combined Oxaliplatin Neuropathy Prevention Trial (CONCEPT) compared continuous administration of FOLFOX to intermittent administration of 8 cycles of FOLFOX plus bevacizumab followed by 8 cycles of maintenance LV/5FU plus bevacizumab and FOLFOX reintroduction plus bevacizumab for 8 cycles. PFS with continuous administration was 7.3 months compared to 12.0 months with the stop-and-go strategy ($P = 0.044$) [34].

Of note, the CAIRO2 study which evaluated cetuximab in combination with XELOX and bevacizumab limited the number of cycles of XELOX to 6 in order to decrease the neurotoxicity of the regimen. The PFS of 10.7 months with a limited number of cycles of combination chemotherapy with bevacizumab was encouraging. However it was not specified if oxaliplatin was subsequently reintroduced or not [35].

III. The complete stop of chemotherapy

The evolution of treatment for colorectal carcinoma has resulted in approximately one year median OS with 5-FU alone, to 16 to 20 months for FOLFOX4, to more than 20 months when patients were exposed to all available drugs. Chemotherapy-free intervals (CFI) are frequently employed in patients with advanced colorectal cancer, for several reasons, including lengthy sustained responses or stabilisation, toxicity, and the patient's decision to discontinue treatment. The gradual prolongation of median survival in patients with metastatic disease and the difficulty to keep patients on therapy for a long time led to the evaluation of chemotherapy discontinuation in prospective trials.

Two studies have evaluated CFI after 5-FU therapy alone [36,37]. The largest study randomised 354 patients. The median duration of CFI was 2.8 months, and there was no deterioration of survival and less toxicity in patients randomised to stop therapy, compared to patients who remained on continuous therapy [37]. However, only 37% of the eligible patients had a reintroduction of their treatment.

Two recent studies evaluated the complete stop of therapy in patients receiving combination chemotherapy. The OPTIMOX2 study compared chemotherapy holiday to maintenance therapy with leucovorin and 5-FU, following 6 cycles of FOLFOX chemotherapy in the first-line treatment of MCRC [38]. Results were in favour of maintenance therapy. The median duration of disease control (DDC), the primary endpoint, was significantly longer in the maintenance arm than in the CFI arm (13.1 versus 9.2 months), with a hazard ratio (HR) of 0.71 (95% CI, 0.51 to 0.99; $P = 0.046$). Maintenance therapy was associated with an increase in the median duration of PFS from 6.6 months

in the CFI arm to 8.6 months in the maintenance arm (HR 0.61, $P = 0.0017$). Median survival was also prolonged in the maintenance arm compared to the CFI arm, 23.8 months versus 19.5 months, respectively (HR 0.88, $P = 0.42$). The 2-year survival rate was 50.0% in the maintenance arm vs. 39.4% in the CFI arm. An important limitation of this study was the randomisation of patients before initial treatment, thus including patients in the intermittent arm who were not eligible for this strategy.

The second study is the MRC COIN study (815 patients per arm) which compared a continuous oxaliplatin-based chemotherapy until disease progression to a complete stop-and-go strategy after 3 months of an oxaliplatin-based treatment [24,39]. Patients in the investigational arm received chemotherapy intermittently for 12 weeks with the reintroduction of chemotherapy for a period of 3 months on progression of the disease.

The risk of death was increased by 9% in the intermittent therapy group (HR 1.09), while the median overall survival was 14.3 months (intermittent) versus 15.3 months (continuous). These data indicate a slight difference in favour of continuing chemotherapy compared to chemotherapy-free intervals. However, a smaller proportion of patients receiving intermittent treatment had grade 3/4 toxicities, including hand–foot syndrome (2% vs. 4%, $P = 0.044$) and peripheral neuropathy (5% vs. 19%, $P = 0.001$). It was suggested that the small difference in survival should be weighed against the significantly reduced toxicity associated with intermittent treatment.

This study, like OPTIMOX2, randomised patients before initial treatment and included ineligible patients to this strategy. We now believe that chemotherapy holidays cannot be decided before therapy is initiated in patients with advanced colorectal cancer. Patients with progressive disease on FOLFOX therapy or amenable to salvage surgery biased the results. Despite these negative results, a significant number of patients can benefit from chemotherapy discontinuation. Our new criteria for chemotherapy discontinuation were defined from patients in the OPTIMOX1 and 2 studies who had a successful CFI and a prolonged survival: a normal CEA level after 3 months of chemotherapy and chemotherapy for at least 6 months before CFI [40].

Evaluation of treatment reintroduction

Oxaliplatin stop and go or complete stop in therapy raise a specific problem of evaluation. Progression-free survival is not an optimal endpoint to evaluate therapeutic strategies in advanced colorectal cancer as the effect of reintroduction is not captured. Therefore, composite endpoints have been proposed to evaluate a chemotherapy strategy when sequential treatments or reintroduction are given: duration of disease control (DDC) and time to failure of strategy (TFS). DDC is defined as the sum of PFS of each active treatment course. DDC excludes intervals between disease progression and reinitiation of treatment and PFS of inactive treatment if PD occurs at first evaluation after treatment reinitiation (either reintroduction in a stop-and-go strategy or subsequent course of treatment in a multi-line strategy). Censoring rules for DDC were: end of study with no PD and addition of new therapeutic agent. Curative surgery for metastasis (R0–R1) was not censored. TFS was defined as beginning with the initiation of the strategy under investigation and ending with the first of the following events: death; disease progression on the last received planned sequence; patient requires the addition of a new therapeutic agent; patient experiences disease progression during a partial or complete break in therapy from initial treatment strategy and receives no further therapy within one month. Censoring rules for TFS were: end of study with neither PD nor new therapy intervention. Curative surgery for metastasis (R0–R1) was not censored. Both endpoints showed similar results and a good correlation with overall survival [41].

Oxaliplatin sensitivity

Defining oxaliplatin sensitivity is of importance for the therapeutical strategy when oxaliplatin reintroduction is scheduled of feasible. As with platinum compounds in ovarian cancer, a prolonged interval between two FOLFOX therapies or a good response to first-line FOLFOX predicted the efficacy of oxaliplatin reintroduction. We performed a pooled analysis of clinical characteristics and survival outcomes of patients from three prospective studies in which oxaliplatin was reintroduced [3,38,42]. Three hundred and thirty patients were included. PFS and OS following reintroduction were both increased in patients whose response and PFS to initial FOLFOX treatment had been greater, and in case of prolonged oxaliplatin-free interval. The median PFS for FOLFOX reintroduction following an oxaliplatin-free interval of <6 months, 6–12 months and >12 months was 3.0 months, 5.0 months and 7.1 months, respectively ($P < 0.0001$). The median OS following an oxaliplatin-free interval of <6 months, 6–12 months and >12 months was 8.9 months, 16.7 months and 22.2 months, respectively ($P < 0.0001$) [43].

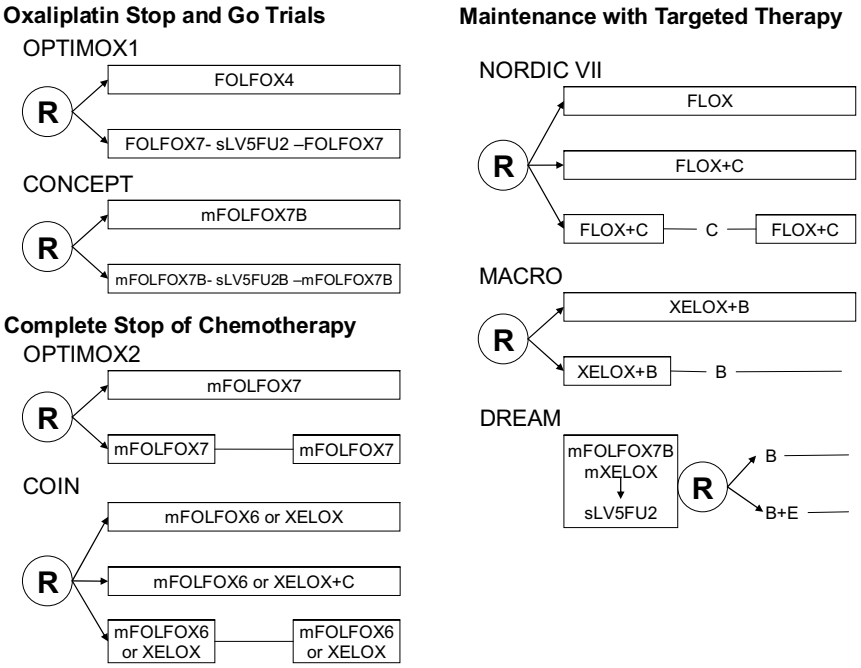

Fig. 2. Trials discussed in the present paper. B: bevacizumab, C: cetuximab, E: erlotinib.

IV. Targeted therapy during maintenance chemotherapy of chemotherapy-free intervals

Recent studies have evaluated maintenance therapy without chemotherapy. Targeted therapies blocking a critical pathway for tumour growth can delay tumour progression with fewer side effects than chemotherapy.

Cetuximab was evaluated in the NORDIC VII study. 566 patients were given LV/5FU bolus/oxaliplatin (FLOX), with or without cetuximab, either continuously or intermittently. OS for patients treated with FLOX intermittently and cetuximab continuously was similar to that of patients treated continuously. Survival was also similar in patients continuously receiving FLOX alone. Remarkably, for an unknown reason, in that trial, the *KRAS* status did not affect the efficacy of cetuximab, which was similar to, or even non-significantly greater than, that in patients with mutated than in patients with wild-type *KRAS* [44].

Bevacizumab was evaluated in the Spanish MACRO trial, which compared, in 480 previously untreated patients, two maintenance therapy regimens, capecitabine + oxaliplatin (XELOX) + bevacizumab and bevacizumab alone [45]. There were no statistically significant differences in PFS (11.0 vs. 10.3 months), OS (25.3 vs. 20.7 months), or metastase resection rate (10.0% vs. 8.3%) between the two groups.

Ongoing studies, like the DREAM trial, are further evaluating the role of targeted therapies alone during chemotherapy discontinuation. The DREAM study compares maintenance therapy with bevacizumab alone, like in the MACRO trial, and maintenance therapy with bevacizumab plus erlotinib. In this trial patients are randomised after 3–6 months of chemotherapy plus bevacizumab, and patients with progressive disease or candidates for metastasis resection after tumour shrinkage are not eligible.

Conclusion

Treatment of metastatic colorectal cancer therapy is not limited to the most active chemotherapy regimens anymore. Chemotherapy and targeted therapies are part of a global strategy also based on biomarkers, evaluation of co-morbidities, sites of the disease and previous adjuvant therapy. This strategy is today using salvage surgery, several lines of therapy, chemotherapy stop and go and chemotherapy-free intervals. The goal is to achieve 30-month median overall survival.

Conflict of interest statement

Consultant or speaker: Roche/Genentech, Sanofi, Merck-Serono

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