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ORIGINAL ARTICLE

The impact of complete chemotherapy stop on the overall survival of patients with advanced colorectal cancer in first-line setting: A meta-analysis of randomized trials

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ABSTRACT

Background. The impact of the duration of chemotherapy on the overall survival of patients with metastatic colorectal cancer (mCRC) is controversial and studies have failed to define a clear standard.

Methods. We searched medical literature databases and oncology conferences proceedings for randomized controlled trials (RCT) that compared the overall survival of mCRC patients who received continuous first-line chemotherapy until disease progression versus those who were offered complete treatment stop after a fixed number of cycles. Studies including targeted agents were also included. A meta-analysis of reported hazard ratios (HRs) for survival was performed.

Results. We retrieved 240 trials, of which six were eligible and five were included in the pooled analysis of overall survival (N = 3061). The overall survival between continuously delivered chemotherapy and complete stop was not statistically different (HR = 0.93, 95% CI 0.85–1.02; p = 0.12; $I^2 = 5\%$). The results are similar when we analyzed separately the trials performing randomization before versus after induction therapy. The median chemotherapy free interval in the complete stop group was 3.9 months (3.6–4.3 months). Chemotherapy administered until progression was associated with more adverse effects and impaired quality of life.

Conclusion. Compared with first-line continuous chemotherapy administered until disease progression, complete treatment stop did not have a detrimental impact on the overall survival of patients with mCRC. Identification of predictive biomarkers could help clinicians to select the patients who would benefit from continuous cancer-directed therapies.

Colorectal cancer (CRC) is the fourth most common cause of cancer-related death worldwide [1]. Although a subset of patients with liver- and/or lung-only metastatic disease, local recurrence, or limited intra-abdominal disease can achieve prolonged disease-free intervals by multimodal treatment, most of patients with metastatic colorectal cancer (mCRC) are incurable. Palliative treatment consists of systemic chemotherapy with fluoropyrimidines in monotherapy or in combination with oxaliplatin or irinotecan [2–7], with or without monoclonal antibodies [8–10]. Multiple studies have proved the benefit of the palliative chemotherapy on overall survival (OS), regardless of sequence used [11,12]. However, optimal treatment duration of chemotherapy is still unknown and interventions to reduce drug-related adverse events and to preserve quality of life are of prime importance. In this context, studies have tested the strategy of intermittent therapy, i.e. allowing patients to enjoy periods of complete chemotherapy cessation. Yet, such studies have failed to define a clear standard and the best treatment schedule is still debatable.

In the stop-and-go approach used in OPTIMOX 1 trial [13], where oxaliplatin-based chemotherapy is delivered for a fixed number of cycles followed by maintenance with fluoropyrimidines until progression,

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when oxaliplatin is reintroduced, has proved as an option of treatment and is widely used in clinical practice. Another strategy to avoid toxicity is to stop chemotherapy completely instead of maintenance with fluoropyrimides. Complete stop of chemotherapy have been studied and also shown offer less toxicity. Randomized clinical trials (RCT) have compared continuously administered versus complete stop of chemotherapy and suggested that chemotherapy-free intervals (CFIs) do not compromise patients' OS. However, there is concern that these studies could have been underpowered to detect smaller but clinically meaningful differences resulting from continuous chemotherapy. In fact, some trials have chosen large effect differences between arms to calculate their sample size, such as absolute gains of 20% in survival rates with continuous treatment [14,15]. A recent published meta-analysis evaluated the evidence comparing continuous chemotherapy to a variety of intermittent strategies of delivering therapies for the first-line treatment of unresectable mCRC [16]. However, they did not include the recently presented phase III trials CAIRO-3 [17] and AIO KRK 0207 [18].

Considering the stated controversy, we have performed a systematic review and meta-analysis of RCTs that compared chemotherapy, with or without targeted agents, administered continuously until disease progression versus complete treatment interruption in the first-line setting for patients with mCRC.

Methods

Search and selection criteria

We performed a systematic review of RCT which compared the OS of first-line chemotherapy delivered continuously until progression versus complete treatment stop for patients with mCRC. Studies of different regimens of chemotherapy (single-agent or combination) as well as combinations of chemotherapy with monoclonal antibodies were included.

First-line treatment until progression could be either a fixed number of cycles with continuation of the same initial treatment until disease progression or a fixed number of cycles of initial induction chemotherapy followed by additional cycles of an alternative cytotoxic chemotherapy regimen.

Articles were screened for eligibility by two independent investigators (AALP and JFMR) followed by a third blinded reviewer (RPR) in case of divergence. OS could have been reported as either the primary or a secondary endpoint. Clinical trials that stopped and reintroduced treatment after a fixed period of time (not when progression was detected) [19] were excluded. Trials assessing the efficacy of maintenance with single-agent monoclonal antibodies were not considered eligible.

The search for full publications was conducted through PubMed, EMBASE and the Cochrane Central Register of Controlled Trials databases. There were no language restrictions. We complemented the search with abstracts and virtual meeting presentations from the American Society of Clinical Oncology conferences (ASCO) and the European Society of Medical Oncology (ESMO) or European Conference of Clinical Oncology (ECCO) meetings. We also hand-searched the reference lists of every primary study for additional publications. Database search was conducted using the following terms, including MeSH descriptors: "Maintenance Chemotherapy" OR "intermittent chemotherapy" AND "colorectal neoplasm", limiting the search to "Randomized Controlled Trial", from date on inception onward until November 2014. During the same time span, we sought eligible trials in the EMBASE database, using the same abovementioned terms, and Cochrane Central Register of Controlled Trials database, using the words "Intermittent chemotherapy" AND Colorectal Cancer". For the ASCO abstracts, we used the terms "Intermittent chemotherapy" AND Colorectal Cancer" and "Maintenance Chemotherapy AND Colorectal Cancer" located in abstract body and/or title of studies presented between January 1998 and June 2014; the ESMO/ECCO abstracts were screened for manually from January 2007 to end of September 2014. We assumed that abstracts published before these dates would already be published in full.

Two investigators (AALP and JFMR) selected the eligible RCT in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20,21]. A third investigator (RPR) was consulted when divergence came up and consensus was achieved for all data.

Data extraction

We extracted the following data independently, using standardized collection forms: journal/conference and year of publication, number of patients planned, accrued and included in the analyses, age, type of first-line chemotherapy, type of second-line treatment used and the percentage of patients who received it, median follow-up, CFI as reported by studies, toxicity information limited to proportion of grade 3 or 4 events, and OS with its respective hazard ratio (HRs) and confidence intervals (CIs). The authors of studies published as abstracts only were contacted in order to provide relevant unpublished data.

Methodological assessment of quality

The assessment of the quality of RCT was made through the criteria suggested by Jadad and colleagues [22], where both study methods and results are evaluated with a quality checklist. Quality criteria include evaluations of the randomization process, concealment of treatment allocation, methods of blinding and handling of dropouts. A resulting global quality score indicates the risk of bias.

Outcome measures

Our primary endpoint was OS as reported in each study. Secondary endpoints were the length of CFI, defined as the time from interruption of chemotherapy until its reintroduction after progression disease, reported data on health-related quality of life (QoL), and information about toxicity. Data about patient-reported outcomes and adverse events were extracted as they were reported, without a standardized manner, given the variability of this information across trials.

Analysis and synthesis

The meta-analysis for pooled OS was performed using RevMan 5.1 software (Cochrane Collaboration Information Management System).

Time-to-event outcomes were compared using HR. Respective 95% CI were calculated for each estimate and presented in forest plots. The pooled HR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95% CI) is the best estimate of the true (pooled) outcome. The effect of the treatment for each single study was expressed as benefits ratios of continuous chemotherapy until disease progression versus complete stop of treatment. Impact measures were estimated based on the number of evaluable patients. Analyses were conducted using a random effect models.

Survival data extraction was preferably performed by the direct collection of original HRs described in the selected trials. When data reported were insufficient, the HR was estimated indirectly, applying either the reported number of events and the corresponding p-value for the log-rank statistics, or by transcription of OS curves. In this case, the original survival curves from electronic publications were enlarged, and data extraction was based on reading off coordinates for each variable, using a spreadsheet provided by Tierney et al. [23].

The heterogeneity between the risk ratios for the same outcome between different studies was assessed using the χ^2-based Q statistic (χ^2), with significance at a p-value of less than 0.10, and expressed in I^2 index. If there was evidence of heterogeneity ($I^2 > 35\%$), we performed a subsequent analysis excluding trials that would be responsible for the heterogeneity based on clinical or methodological factors and possible explanations were investigated and reported. Results were expressed as HRs with 95% CIs. An $HR < 1.0$ favored the continuous treatment group, i.e. it indicated that patients receiving continuous treatment until disease progression had a lower probability of experiencing an event (death).

Results

Results of search strategy

The search resulted in 240 entries, of which 78 duplicated records were removed. From the remaining 162 studies, 156 were excluded as shown in Figure 1. Six trials met the predefined criteria, totaling 3100 patients [14,15,17,18,24,25]. Both MRC COIN trial and AIO KRK 0207 trial had originally three arms and the maintenance arms of monoclonal antibody only were not considered in this pooled analysis.

Characteristics of eligible trials

The characteristics of the six eligible studies are summarized in Table I. The median number of patients per trial was N = 336 (range 39–1630). Median follow-up periods ranged from 13 to 48 months. OS was the primary outcome in three of the six trials [15,24,25].

All RCTs compared continuous first-line treatment until disease progression with complete stop after an induction period that varied from 12 to 24 weeks. In the CAIRO-3 trial, investigators treated all patients with six cycles of CAPOX plus bevacizumab (18 weeks) and for those who did not progress at this point, randomization was performed to continue treatment or complete stop. In the AIO KRK 0207 trial, patients without progressive disease were randomized after an induction period of 24 weeks. In all other studies, induction period lasted 12 weeks. All but one trial used an oxaliplatin-based regime as induction chemotherapy [15] and two utilized chemotherapy combined with monoclonal antibodies. Two trials used a non-inferiority design [18,24]. According to the quality criteria [22], three of six trials were classified as containing high risk of bias (Table I). These RCT were included in the analysis because the major criteria for high risk of bias related to trials published in abstract form, where detailed information was not available.

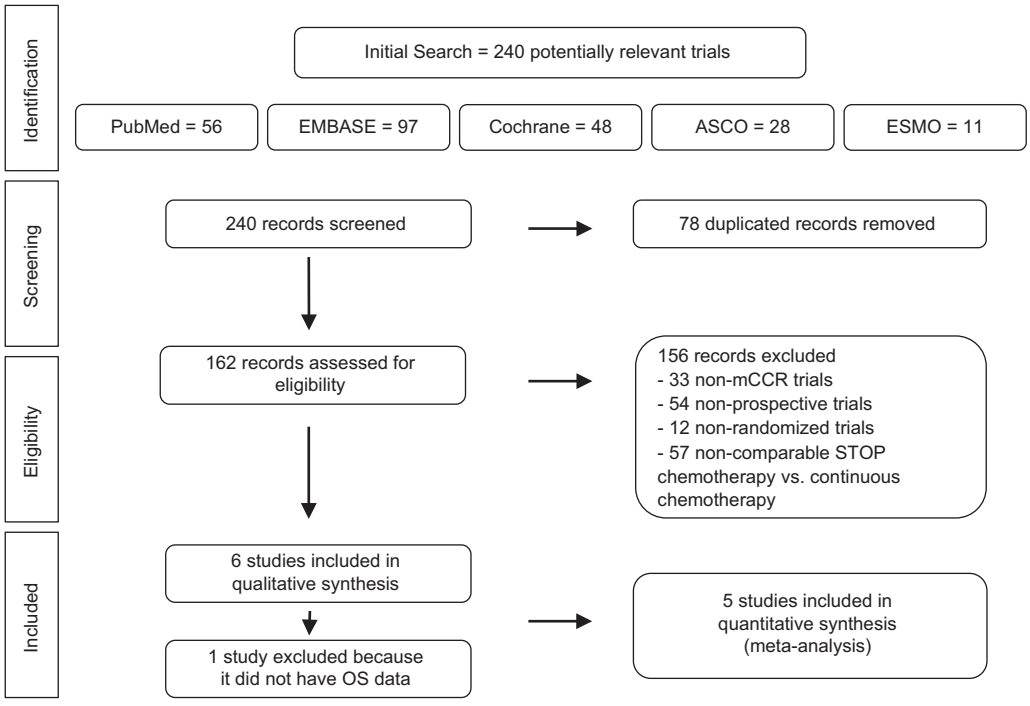

Figure 1. Results of search for eligible trials (PRISMA Fluxogram). ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; mCCR, metastatic colorectal cancer.

Overall survival

Four trials measured OS from the date of randomization to date of death from any cause [15,17,18,24], one trial did not describe how survival was calculated [25] and another trial did not explain from which date, from randomization or from date of first treatment, survival was measured [14]. Time of random assignment was from the start of the induction chemotherapy in two trials [14,24] and after an induction period in four trials [15,17,18,25]. Subgroup pooled analyses were performed according to time of randomization.

Five randomized trials were included in the meta-analysis, with a total of 3061 patients; one trial did not report extractable data related to OS and it was excluded [25]. The meta-analysis showed no significant difference in OS between chemotherapy delivered continuously until tumor progression versus complete stop (HR = 0.93, 95% CI 0.85–1.02; p = 0.12) with low heterogeneity across trials (I^2 = 5%; p = 0.38; Figure 2). The MRC COIN Trial [24] reported a HR of 1.084 favoring the continuous chemotherapy group. This ratio was appropriately adjusted for analysis, considering the HR of the continuous-chemotherapy arm over the complete stop strategy arm (HR 0.92). Similarly, we have adjusted the HR of the trial by Maughan et al. [15], which originally reported a HR of 0.87 favoring intermittent.

In order to evaluate potential selection bias in the studies randomizing patients only after induction, we performed subgroup analyses according to timing of randomization. The pooled analysis of the two trials that randomized patients right at the start of first-line treatment [14,24] found similar results: HR: 0.92 (CI 95% 0.63–1.23; p = 0.13) without heterogeneity between trials (I^2 = 0%; Figure 2). The analysis of RCT where randomization was done after induction showed evidence of heterogeneity (I^2 = 50%; Figure 2). As a result of the outlier OS result of the Maughan et al. [15], the only trial that used a single-agent induction was identified as a source of heterogeneity, and a sensitivity analysis was performed excluding this trial. This subsequent meta-analysis, with only trials which used combination chemotherapy induction, resulted marginally positive for OS in favor of chemotherapy delivered continuously until tumor progression with a relative reduction in mortality of 10% (HR = 0.90, 95% CI 0.82–0.99; p = 0.02) and with no heterogeneity among trials (I^2 = 0%; p = 0.59; Figure 3).

Chemotherapy-free intervals and progression outcomes

In all included trials, patients who had not progressed after a fixed number of cycles started a CFI until evidence of disease progression, when the same treatment was restarted. The range of CFI was

Table I. Selected trials characteristics and risk of bias.

Characteristics	Maughan, 2003	Chibaudel, 2009 (OPTIMOX2)	Alexopoulos, 2006	Adams, 2011 (MRC COIN)	Koopman, 2014 (CAIRO 3)	Hegewisch-Becker, 2014 (AIO KRK 0207)
Number of patients, planned	420	200	Not described	1614	Not described	Not described
Number of patients, randomized	354	202	39	1630	558	317[c]
Age-median	64 years	67 years	69 years	63 years	NI	65
Type of trial	Superiority	Superiority	Superiority	Non-inferiority	Superiority	Non-inferiority
Initial chemotherapy regimen	Infusional 5-FU or raltitrexed	mFOLFOX7	FOLFIRI	FOLFOX or CAPOX	CAPOX[c] Bev	5-FU[c] Oxaliplatin[a,c] bev
Induction treatment time	12 weeks	12 weeks	12 weeks	12 weeks	18 weeks	24 weeks
Continuous treatment	Same as initial	Infusional 5-FU	Same as initial	Same as initial	Cap[c] bev	5-FU[c] bev (or Bev alone)
Time of randomization	After induction	Before induction	After induction	Before induction	After induction	After induction
Primary endpoint	OS	Disease-control rate	OS and TTP	OS	PFS	TFS
Secondary endpoints	PFS, QoL, toxicity, RR	OS, PFS, RR	–	PFS, toxicity, RR, QoL	OS, TTP	PFS, OS, toxicity, QoL
Median survival: Continuous vs. complete stop	11.3 vs. 10.8 months	23.8 vs. 19.5 months	21 vs. 15 months	15.8 vs. 14.4 months	21.6 vs. 18.1 months	23.4 (and 22.6) vs. 23.3 months
HR for survival (95% CI)	HR = 1.15; 95% CI (0.91–1.46)	HR = 0.88; 95% CI (0.63–1.23)	NI	HR = 0.92; 95% CI (0.82–1.04)	HR = 0.85; 95% CI (0.71–1.02)	HR = 0.94; 95% CI (0.68–1.29)
Median time to progression 1st line	4.9 vs. 3.7 months	13.1 vs. 9.2 months	8.0 vs. 9.0 months	8.4 vs. 7.4 months	11.7 vs. 8.5 months	6.8 and 6.2 vs. 6.4 months
HR for progression 1st line (95% CI)	HR = 0.84; 95% CI (0.67–1.04)	HR = 0.71; 95% CI (0.51–0.99)	NI	HR = 0.95; 95% CI (0.86–1.06)	HR = 0.67; 95% CI (0.56–0.81)	HR = 0.79; 95% CI (0.62–1.00)
Chemotherapy-free interval (complete stop group)	4.3 months	3.9 months	NI	3.7 months	4.1 months	3.6 months
Duration of treatment in continuous group	3.0 months	4.8 months	NI	7.5 months	NI	NI
Proportion of patients in complete stop group who restarted treatment as planned	37%	79%	NI	64%	60%	45%
Proportion of patients who received 2nd line therapy (continuous group)	30%	63%	52%	62%	NI	NI
Proportion of patients who received 2nd line therapy (complete stop group)	35%	51%	35%	52%	NI	NI
Median follow-up	16.8 months	40.7 months	13 months	20.9 (continuous) and 21.8 months (intermittent)	48 months	27 months
Quality evaluation[b]						
Randomization process	Adequate	Adequate	Not described	Adequate	Not described	Not described
Withdrawals	Described	Described	Described	Described	Not described	Described
Double-blinded	No	No	No	No	No	No
Risk of bias[a]	Low	Low	High	Low	High	High

[a]mFOLFOX6, FOLFOX4 or CAPOX; [b] Adapted from Jadad AR, Moore RA, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12; [c] Without 156 patients from Bevacizumab alone arm.
Bev, bevacizumab; Cap, capecitabine; FFS, failure-free survival; NI, not informed; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RR, response rate; TFS, time to failure strategy; TTF, time to failure.

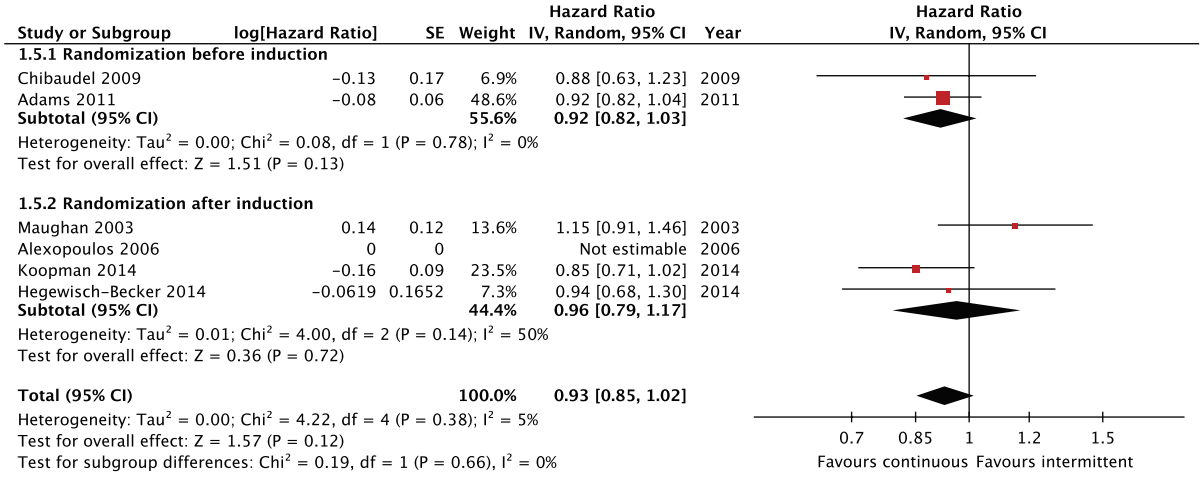

Figure 2. Forest plot of overall survival with 3061 patients.

3.6–4.3 months. Only a proportion of patients randomized to the complete stop groups in each study restarted the same regimen after the treatment pause as previous planned: 37% (66 of 178) in the Maughan et al. study [15], 79% (66 of 108) in OPTIMOX-2 [14], 64% (325 of 511) in MRC-COIN [24], 60% (168 of 279) in the CAIRO-3 [17] and 45% in AIO KRK0207 trial [18] (Table I).

The timing for the evaluation of progression varied across trials and thus, could not be adequately pooled for analysis. In the OTIMOX-2 [14], computed tomography (CT) scans were performed within 21 days of inclusion and evaluations were repeated after eight and 12 weeks, and every eight weeks thereafter. In the MRC COIN [24] patients were assessed clinically at least every six weeks and radiologically at every 12 weeks. Maughan et al. [15] required follow-up reports every six weeks and included details of treatment, symptoms, response, and progression. The AIO KRK 0207 trial evaluated tumor response and toxicity every six weeks. The OPTIMOX-2, MRC COIN trial evaluated tumor progression according to RECIST 1.0 [26] and two trials did not describe the follow-up schedule [17,25].

Health-related QoL and toxicity

Four trials reported data on health-related QoL [15,17,18,24] and, because they used different instruments, we were unable to statistically pool the results (Table II). In the trial by Maughan et al. [15], patients completed the hospital anxiety and depression scale questionnaire (HADS) [27] and the European Organization for Research Treatment of Cancer (EORTC) quality of life questionnaire (QLQ C30) [28]. Patients on continuous chemotherapy reported more chemotherapy-related side effects (dry or sore mouth, discomfort with hand and feet) than did those patients who stopped treatment. Despite this difference, the groups were similar in terms of physical functioning and overall

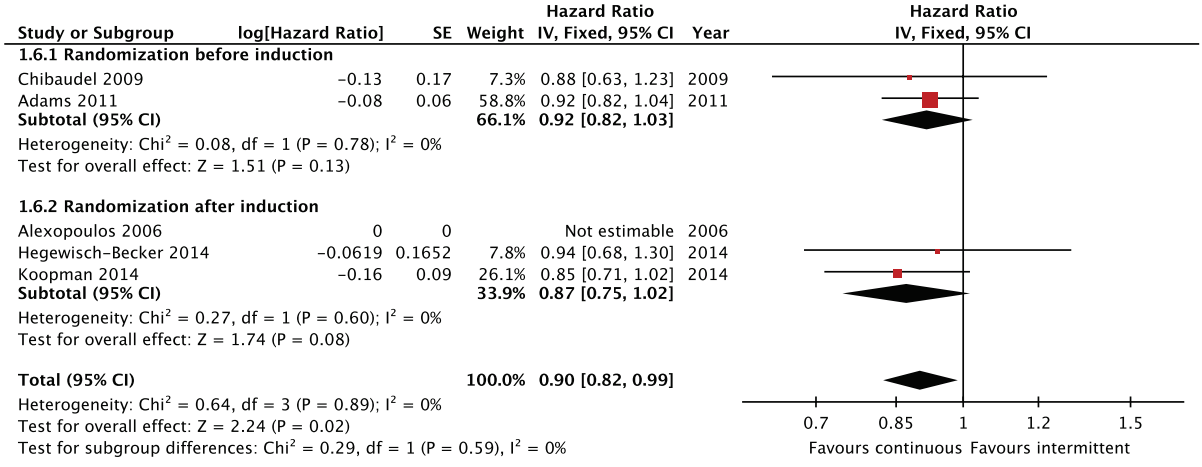

Figure 3. Forest plot of overall survival – only trials with combination chemotherapy induction.

Table II. Quality of life and main grade 3–4 toxicities reported.

		Quality of life (QoL)		Most common grade 3 or 4 Non-hematological toxcities					Grade 3 or 4 Hematological toxcities		
Study	Arm	QoL instruments	QoL findings	Neuropathy	Hand-Foot Syndrome	Mucositis	Diarrhea	Vomiting	Thrombo-cytopenia	Neutropenia	Anemia
Maughan, 2003	Complete stop	HADS, QLQ-C30	No difference. Patients in continuous group had more AE	NR	2%	NR	6%	7%	1%	4%	1%
	Continuous			NR	4%	NR	10%	5%	1%	2%	5%
Chibaudel, 2009 (OPTIMOX2)	Complete stop	NR	NR	4.9%	0%	1.9%	3.9%	3.9%	3.9%	11.7%	0%
	Continuous			2.9%	0%	1.0%	3.1%	1.0%	8.2%	21.4%	0%
Alexopoulos, 2006	Complete stop	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Continuous			NR	NR	NR	NR	NR	NR	NR	NR
Adams, 2011 (MRC COIN)	Complete stop	NCI-CTC, QLQ-C30	Favored complete stop	5%	3%	1%	10%	4%	3%	8%	3%
	Continuous			27% ($p < 0.001$)	5%	1%	8%	2%	1%	12% ($p = 0.03$)	1%
Koopman, 2014 (CAIRO 3)	Complete stop	NR	Favored complete stop but not clinically relevant	NR	NR	NR	NR	NR	NR	NR	NR
	Continuous			NR	NR	NR	NR	NR	NR	NR	NR
Hegewisch-Becker, 2014 (AIO KRK 0207)	Complete stop	QLQ-C30, QLQ-CR29, FoP questionnaire	No difference	NR	NR	NR	NR	NR	NR	NR	NR
	Continuous			NR	NR	NR	NR	NR	NR	NR	NR

AE, adverse effects; CT, chemotherapy; FoP, fear of progression.

health. There was one patient who developed a treatment-related fatal adverse event.

In the MRC COIN trial [24], symptoms were assessed throughout treatment with the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC version 3.0) and the QLQ-C30 questionnaire. Grade 3 or worse neutropenia (12% vs. 8%) and grade 3 or worse peripheral neuropathy (27% vs. 5%, $p < 0.0001$) were more frequent in the continuous treatment group. There was a significant benefit from complete chemotherapy stop at 24 weeks in terms of less fatigue, dry or sore mouth, less interference with daily activities, less nausea or vomiting, improved appetite, less constipation, and less diarrhea ($p < 0.05$ for all) [24]. Complete chemotherapy stop also was beneficial in terms of self-perceived functioning role ($p = 0.015$) and social functioning ($p = 0.016$). Two percent of the total deaths were reportedly associated with chemotherapy, regardless of treatment group.

The AIO KRK 0207 trial [18] assessed patients' QoL, using the EORTC QLQ-C30, the colorectal module QLQ-CR29, and fear of progression (FoP), a validated patient-reported scale, during induction and maintenance therapy at every six weeks. There was no difference in either QoL or FoP among the trial arms.

The OPTIMOX-2 trial [14] showed a non-significant increase in grade 3–4 hand-foot syndrome and thrombocytopenia in the continuous treatment group [20]. In the CAIRO-3 trial [17], QoL was assessed throughout the study. There was a statistically significant difference in favor of the therapeutic pause ($p = 0.004$), which was not considered to be clinically relevant. This trial provided no information in its abstract about QoL instruments used.

Discussion

The present meta-analysis of RCTs showed no significant difference in OS between first-line chemotherapy continuously administered until disease progression and complete treatment stop for patients with mCRC. Even when subgroup analyses based on time of randomization were performed, the pooled OS results remained similar. Noteworthy, complete treatment stop seemed to be associated with less toxicity and better quality of life.

Complete chemotherapy stop is a pragmatic and clinically important issue that often comes up during

the treatment of patients with metastatic solid tumors. In breast and prostate cancer, e.g. the use of intermittent hormones or cytotoxic agents has not compromised patients' survival [29–31]. In non-small cell lung cancer (NSCLC), a meta-analysis has demonstrated that extending chemotherapy beyond 4–6 cycles may delay disease progression, without benefit on OS [32,33].

In contrast, two of four RCT in our study showed that complete chemotherapy interruption was associated with less toxicity and better QoL [15,24] (Table II). For example, the MRC COIN study [24] demonstrated that stopping chemotherapy was associated with less hospital visits and with better mean scores of fatigue, pain, dyspnea, appetite loss, constipation, and global QoL. Similarly, the meta-analysis of NSCLC trials showed that prolonging treatment led to more toxicity which impaired patients' QoL [32]. Even in clinical trials where the protocols specify that treatment has to be delivered until progression, many patients are given a treatment break due to toxicity [8].

Despite our results, continuous treatment resulted in a numerical improvement in survival in most studies, and was associated with a tendency towards prolonged time to tumor progression. It is possible that some patients who stopped chemotherapy had worse outcomes because they had not achieved maximum tumor response and, thus, could have benefited from longer treatment. Also, many of these patients were not rechallenged with oxaliplatin at the time of progression (37–79%) [14,15,17,18,24]. Retrospective studies have suggested that retreatment with oxaliplatin is associated with survival gains [34]. While the delivery of more than six months of chemotherapy is apparently ineffective in patients with advanced NSCLC [32,35], the number of cycles necessary to achieve the maximum survival benefit in mCRC is still unknown.

Five RCTs included used combination of fluoropyrimidine with either oxaliplatin or irinotecan [14,17,18,24,25], and two of the six trials included combination of chemotherapy and a monoclonal antibody [17,18] (Table I). Given that fluoropyrimidine monotherapy is an acceptable option for first-line therapy [11,12] and that FOLFIRI and FOLFOX are equally effective in this scenario [36], we considered that our findings are generalizable to current practice.

Recent trials have asked the question of whether maintenance therapy with bevacizumab [18,29,37,38] or cetuximab alone [39] could have the same efficacy as polychemotherapy combined with an antibody given until progression. A recent meta-analysis of RCT that compared first-line continuous chemotherapy to a variety of intermittent therapies for mCRC also did not find any statistically significant differences that could favor a maintenance therapy with targeted agents [16]. Differently from that meta-analysis, we evaluated only trials that had a complete treatment stop arm; besides, we included the final results of the CAIRO-3 trial [17] and also the mature survival data from recent AIO KRK 0207 trial [18].

Our results have some limitations. Three RCT were presented only in abstract form, and one trial, unfortunately, did not report the survival curves or the relative difference (HR) for OS [25]. There was a lack of standardized definition of progression across trials, what has prevented us from pooling the median time to progression or the accurate CFI. We used published results instead individual patient data. Even though individual data would make results more accurate [40], we believe it is unlikely that it would change our findings because our primary endpoint, survival, is a hard outcome with low risk of measurement/evaluation biases. Additionally, there were some differences across the eligible studies that should be taken into account (Table I): study design (non-inferiority vs. superiority and 2 vs. 3 arms), time of randomization (before vs. after induction), duration of induction treatment and utilization of targeted drugs. However, despite such differences, there was not heterogeneity across trials in both subgroups and final analyses. To our knowledge, this the best available evidence about the impact of complete treatment stop on OS in mCRC.

Many patients seem to benefit from complete chemotherapy interruption. However, how to select these patients is still unknown. Based on a retrospective study, a subset of patients with mCRC benefited from stopping chemotherapy: patients with normal platelet count at baseline and/or patients with normal CEA level after three months of starting oxaliplatin-based chemotherapy [41]. Interestingly, raised platelet count has been previously identified as a poor prognostic marker in mCRC [42]. In the MRC COIN trial [24], patients with elevated platelet count at baseline had substantially inferior survival when managed with complete chemotherapy stop. In addition, subgroup analysis from CAIRO-3 trial found that among patients with complete or partial response, the median OS on the complete stop group was 18.8 months compared with 24.1 months in the maintenance group; for patients with stable disease, the median OS was 15.2 months in the complete stop arm and 16.9 months for patients in the maintenance group [17]. These exploratory findings suggest that tumor response may be a surrogate for a continuous or maintenance strategy. However, it remains to be prospectively validated whether thrombocytosis or response rate

should be used as a decision factor to offer mCRC patients complete treatment interruptions.

In conclusion, we have shown that, compared to complete treatment stop, first-line chemotherapy administered continuously until disease progression did not benefit mCRC patients in terms of OS. In fact, continuous treatment was associated with increased toxicity. Therefore, we strongly feel that complete treatment stop remains a good option for individualized patients. We suggest that patients should be treated until maximum response, which could be between three and six months, although the number of cycles to achieve maximum response has not been established in mCRC and this number varies according to patients and tumor characteristics. After that point, the strategy of complete treatment stop could be discussed with patients. mCRC is a heterogeneous disease with various molecular subtypes identified [43,44]. Molecular profiling of patients with mCRC might be a powerful tool to stratify patients who might benefit from a more aggressive therapy, such as continuous treatment, as well as to identify patients with more indolent disease, where complete chemotherapy stop could be safely offered. Prospective collection of tumor tissue as part of phase III trials comprises a smart approach to identify predictive markers in mCRC and to help clinicians tailor the management of this disease.

Declaration of interest: All authors declare that we have no conflicts of interest in the authorship or publication of this contribution.

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