Optimal duration of a first-line palliative chemotherapy in disseminated colorectal cancer – a review of the literature from a developing country perspective

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We still do not know whether the presently used protocol of the first-line palliative treatment of disseminated colorectal cancer (FOLFOX/FOLFIRI protocol) allows maximization of therapeutic response and minimization of side effects. No-one has verified whether continuation of the first-line chemotherapy despite the lack of progression is reflected by improved prognosis or significant risk of toxicity. This issue is of vital importance in the case of developing countries where targeted therapies are not available due to financial shortages. We have identified three potential strategies of the palliative therapy of disseminated colorectal cancer: 1) discontinuation of chemotherapy after a fixed number of cycles with its restart on progression (stop-and-go strategy), 2) intermittent protocol of chemotherapy, and 3) continuation of chemotherapy with discontinuation of the most toxic agent. None of the studies proved the superiority of the most commonly used standard, i.e. 12 cycles of the FOLFOX or FOLFIRI regimen. Although longer duration of this treatment may be associated with higher response rates and longer progression-free survival, these improvements frequently prove insignificant on statistical analysis.

Key words: colorectal cancer, recurrence, overall survival, progression-free survival.

Contemp Oncol (Pozn) 2016; 20 (3): 210–214
DOI:10.5114/wo.2016.61561

Introduction

Colorectal cancer is the second most prevalent solid tumor among male and female patients from developed countries, and the second most frequent cause of mortality in patients of both genders [1]. Due to their oligosymptomatic character, many cases of colorectal cancer are diagnosed at advanced stages, which is reflected by unfavorable prognosis and poor therapeutic outcomes. Response rates of patients with disseminated colorectal cancer treated with chemotherapy do not exceed 50%, and duration of progression-free and overall survival approximates one year and two years, respectively [2].

Although successful attempts of targeted therapies in disseminated colorectal cancer have been undertaken during recent years, palliative systemic therapy without biological agents still remains a therapeutic standard for about 75% of the patients, especially those from developing countries [3]. The classic regimen of palliative therapy for disseminated colorectal cancer usually comprises 12 (more rarely 6) cycles of treatment according to the FOLFOX/FOLFIRI protocol, with subsequent discontinuation of chemotherapy and waiting until progression [2]. However, such an attitude raises a growing number of concerns, as we still do not know whether the presently used protocol of the first-line palliative treatment allows maximization of therapeutic response and minimization of side effects [4]. In other words, no-one has verified whether continuation of the first-line chemotherapy despite the lack of progression is reflected by improved prognosis. On the other hand, it is also unclear whether the continuation of chemotherapy despite the lack of progression is associated with a significant risk of enhanced toxicity [2]. While treatment with biological agents is usually continued until disease progression after a couple of months of combined biological therapy and chemotherapy, the optimal duration of treatment with cytotoxic agents alone has never been precisely established. Furthermore, such studies will probably never be conducted due to the introduction of monoclonal antibodies in metastatic colon cancer patients. Consequently, the purpose of this review is an attempt to identify an optimal duration of first-line palliative chemotherapy in patients with disseminated colorectal cancer.

Searching through the results of recent studies dealing with the palliative therapy of disseminated colorectal cancer, we have identified three potential strategies of treatment: 1) discontinuation of chemotherapy after a fixed number of cycles with its restart on progression (stop-and-go strategy), 2) intermittent protocol of chemotherapy, and 3) continuation of chemotherapy with discontinuation of the most toxic agent [4].

Stop-and-go strategy

The stop-and-go strategy has been a subject of three studies: 1) the MRCC trial [5], 2) the Optimox 2 trial [6], and 3) the MRC-COIN study [7].

The results of the MRCC trial were published in 2003 [5]. Prior to the study, no trials were undertaken in order to establish the optimal duration of treatment in advanced colorectal cancer. However, randomized trials in other malignancies have generally shown that short-course treatment is as effective as long-course [8–23], although some patients receiving short-course chemotherapy might have a shorter time to disease progression [17, 20, 21, 23–25]. Therefore, the authors of the MRCC study verified whether the outcomes of the stop-and-go strategy, namely, stopping chemotherapy after 12 weeks of treatment with the intention of re-challenging with the same regimen on progression, are as effective as those of continuous treatment with the same chemotherapy until progression. Special attention was paid to the time to progression after implementation of both strategies. The inclusion criteria of the study were: primary carcinoma of the colon or rectum, inoperable local or metastatic disease, stable or responding disease (WHO criteria) after 12 weeks of first-line chemotherapy, no previous chemotherapy for metastatic disease, adequate bone-marrow function and renal function, and WHO performance status of 0–2. The treatment regimens included: 1) intravenous calcium folinate 200 mg/m^2 (maximum 350 mg) over 2 hours, followed by fluorouracil 400 mg/m^2 bolus over 5 minutes and fluorouracil infusion 600 mg/m^2 over 22 h, repeated on day 2, with cycles every 2 weeks [26], 2) continuous intravenous infusion of fluorouracil 300 mg/m^2 per day, given through an ambulatory pump [27], or 3) raltitrexed (3 mg/m^2) given intravenously over 15 minutes every 3 weeks [28]. The first group of patients received treatment with the stop-and-go strategy: the treatment was stopped after six cycles and the patients were reviewed every 6 weeks, with radiological assessment of response every 12 weeks. In the case of progression the treatment was restarted with the same regimen as previously. The second group of patients received the same treatment continuously, with a clinical review every 6 weeks, and with radiological assessment of response every 12 weeks. The treatment was stopped only in the case of progression, unacceptable toxic effects, or patient choice. A total of 354 patients were randomized: 178 to the stop-and-go group, and 176 to the continuous arm. Median overall survival for the stop-and-go and continuous groups was 10.8 months and 11.3 months, respectively (p = 0.23), and median progression-free survival equaled 3.7 months and 4.9 months, respectively (p = 0.10). Patients receiving the continuous chemotherapy regimen reported more specific chemotherapy-related toxicity than those in the stop-and-go arm. Consequently, the authors concluded that continuation of the first-line palliative chemotherapy is not associated with statistically significant additional therapeutic benefits or lower toxicity [5].

As the quality of life is an essential factor in the palliative setting, preventing accumulation of side effects of chemotherapy is as important as other treatment end points, such as overall survival and progression-free survival. Moreover, improved quality of life may be reflected by greater efficacy of the second-line treatment in the case of progression of disseminated colorectal cancer [29, 30]. The Optimox 2 study, the results of which were published in 2009, was another trial which explored the stop-and-go strategy [6]. The inclusion criteria of the study were: adenocarcinoma of the colon or the rectum, non-resectable metastases, at least one measurable or evaluable lesion according to RECIST [31], alkaline phosphatase less than 5 × the upper limit of normal (ULN) and creatinine ≤ 3 × ULN, WHO performance status 0 to 2, age 18 to 80 years, and no previous chemotherapy for metastatic disease. Patients were randomly assigned to induction FOLFOX chemotherapy, followed by maintenance therapy with leucovorin plus bolus and infusional fluorouracil until progression (arm 1) or by a chemotherapy-free interval (arm 2); re-induction of FOLFOX was scheduled after tumor progression in either group. In both arms, induction chemotherapy comprised six cycles (3 months) of a modified FOLFOX7 regimen. The primary end point of the study was duration of disease control (DDC), which was defined as progression-free survival (PFS), or, if FOLFOX was reintroduced, the sum of the initial PFS and the PFS of the reintroduction, except in case of progression at the first evaluation after FOLFOX reintroduction [32]. The median DDC turned out to be significantly longer in the maintenance arm than in the stop-and-go arm (13.1 months vs. 9.2 months; hazard ratio HR = 0.71; 95% CI: 0.51–0.99; p = 0.046). Median survival in arm 1 was 23.8 months vs. 19.5 months in arm 2 (HR = 0.88; p = 0.42). Maintenance therapy was associated with an increase in the median duration of PFS: 8.6 months in arm 1 vs. 6.6 months in arm 2 (HR = 0.61; p = 0.0017) [6]. Consequently, this study showed that continuation of the first-line treatment until progression can be reflected by improved therapeutic outcomes: longer progression-free survival and duration of disease control. However, the authors of the Optimox 2 trial did not analyze additional toxicity associated with the prolonged treatment; this is a potential limitation of their findings.

The MRC-COIN trial is another study which verified whether the stop-and-go strategy is non-inferior to continuous treatment in terms of overall survival [7]. All enrolled patients had measurable, inoperable colorectal adenocarcinoma, received no prior chemotherapy for metastases, had WHO performance status 0–2, and had good organ function. The participants were randomized to two arms: 1) oxaliplatin + fluorouracil/leucovorin every other week or oxaliplatin + capecitabine every third week, continued until treatment failure, and 2) the same regimen given for 3 months initially, with further 3-month therapy on progression (stop-and-go strategy). A total of 1630 patients were randomized. The intention-to-treat (ITT) analysis showed a 9% increase in the hazard of death in patients on the stop-and-go treatment (HR = 1.09, with a one-sided upper 90% CI of 1.17; this just exceeded the pre-specified boundary). Median overall survival of patients receiving continuous therapy and those treated with the stop-and-go strategy was 15.6 months and 14.3 months, respectively, and the estimated 2-year survival was 28.3% and 26.1%,

respectively. In the per-protocol analysis (PPA, n = 1103) the HR of death was 1.10 with an upper 90% CI of 1.21. Median overall survival on maintenance and stop-and-go protocols was 19.1 months and 17.6 months, respectively, and the estimated 2-year survival rates were 34.8% and 31.1%, respectively. Noticeably, the study revealed that a raised baseline platelet count, defined as ≥ 400 000 per µl (present in 28% of the patients), was associated with poor survival with stop-and-go chemotherapy. Furthermore, the stop-and-go strategy turned out to be associated with significantly lower toxicity expressed as the prevalence of hand-foot syndrome (2% vs. 4%, p = 0.044) and G3/4 peripheral neuropathy (5% vs. 19%, p < 0.001). No evidence of differences in treatment-related (1.2% vs. 1.2%, p = 0.999) or 60-day all-cause mortality (4.2% vs. 4.4%, p = 0.810) were observed [7]. In conclusion, the MRC-COIN trial showed that maintenance chemotherapy of disseminated colorectal cancer is not always associated with improved prognosis in all patients. While continuation of the first-line chemotherapy can be beneficial in persons in good general status (manifested by normal platelet count), it does not decrease mortality risk in individuals with elevated platelets. Consequently, continuation of the first-line treatment until progression may be advisable only providing proper qualification of patients.

Intermittent chemotherapy

The efficacy and safety of the intermittent protocol of maintenance chemotherapy were analyzed by the Italian GISCAD trial [33]. Apart from the accumulation of side effects, long-term chemotherapy was revealed to be associated with the development of resistance to an administered drug. The results of *in vitro* studies suggest that intermittent administration of 5-fluorouracil (with 2-month pauses) doubles the period before occurrence of resistance to this agent [34]. The aim of the GISCAD trial was to evaluate whether intermittent FOLFIRI chemotherapy is at least as effective as continuous treatment with the same regimen in advanced, previously untreated, colorectal cancer. Inclusion criteria included histologically proven advanced colorectal cancer with the possibility of objective clinical and radiological evaluation, Eastern Cooperative Oncology Group performance status 0 to 2, life expectancy ≥ 3 months, age > 18 years without upper limits, no history of previous chemotherapy apart from adjuvant treatment not including levo-leucovorin + 5-fluorouracil + irinotecan (CPT-11) and terminated at least 6 months before, and adequate bone marrow, renal and hepatic function. All patients received 2 months (4 cycles) of FOLFIRI chemotherapy, and thereafter they were evaluated for objective response. Individuals with complete response (CR), partial response (PR) or stable disease (SD) were randomized to one of two arms. In the intermittent arm, treatment was discontinued for 2 months and thereafter, without further disease evaluation, patients received 2 months (four cycles) of chemotherapy. At the sixth month, a second objective evaluation was carried out: if a progressive disease (PD) was documented, a second-line chemotherapy was instituted, whereas in the other cases, the front-line treatment was continued 2 months off and 2 months on with objective reevaluation every 4 months. In the continuous arm, the treatment was carried out until PD, with objective re-evaluation every 4 months. The regimen employed in the trial was as follows: day 1: CPT-11, 180 mg/m^2, *i.v.* infusion in 30–60 minutes; days 1 and 2: levo-leucovorin, 100 mg/m^2, 2-hour *i.v.* infusion, immediately followed by 5-fluorouracil, 400 mg/m^2 *i.v.* bolus (3–5 minutes) and, immediately after, 600 mg/m^2 in 22-hour *i.v.* infusion. All the drugs were recycled every 14 days, so two cycles were given every month. A total of 337 patients were randomly assigned: 167 (49.6%) to the intermittent arm and 170 (50.4%) to the continuous arm. According to a per-protocol approach, the analysis was conducted on 293 patients, 147 (50.2%) in the intermittent arm and 146 (49.8%) in the continuous arm. The 24-month overall survival rate was 30% for the continuous arm and 34% for the intermittent arm, while median survival was 17 and 18 months, respectively (HR = 0.88; 95% CI: 0.69–1.14). Therefore, the null hypothesis of the inferiority of the intermittent treatment was rejected (p = 0.0008). Also the results of the multivariate analysis, after adjustment for covariates, were similar (HR = 0.87; 95% CI: 0.67–1.12; p = 0.0005). The 12-month progression-free survival rate was 16% for the continuous arm and 18% for the intermittent arm, while median progression-free survival was 6 months for both arms (HR = 1.03; 95% CI: 0.81–1.29). Also the results of the multivariate analysis, after adjustment for covariates, were similar (HR = 1.03; 95% CI: 0.81–1.30). Sensitivity analysis showed that results obtained by intent-to-treat approach were similar for both overall survival (HR = 0.91; 95% CI: 0.72–1.15) and progression-free survival (HR = 0.98; 95% CI: 0.79–1.21). For all types of toxicity, there was no difference in the two treatment arms for the worst toxicity grade experienced by each patient (n = 332), as well as for the proportion of cycles with a grade 3–4 toxicity: 86 cycles out of 764 (11%) and 70 out of 601 (11%), for continuous and intermittent arms, respectively. In conclusion, this study revealed that continuation of intermittent chemotherapy (so-called "chemotherapy holidays") until progression is not associated with worse prognosis, and the subjectively assessed quality of life of patients administered this protocol is probably improved [33]. Furthermore, the cost of intermittent treatment is undoubtedly lower; however, to the best of our knowledge, this issue was not a subject of cost-effectiveness analysis.

Discontinuation of oxaliplatin

The continuation of maintenance chemotherapy with discontinuation of the most toxic agent, oxaliplatin, was the subject of the Optimox 1 trial [32].

The study investigated the use of oxaliplatin discontinuation and reintroduction in a novel stop-and-go strategy consisting of the FOLFOX7 regimen administered for six 2-week cycles followed by 12 cycles of maintenance therapy without oxaliplatin, and subsequent reintroduction of FOLFOX7 for another six cycles. This regimen was compared with the FOLFOX4 regimen (control arm), administered until progression or occurrence of unacceptable

toxicity. The inclusion criteria were: colorectal adenocarcinoma, presence of non-resectable metastases, at least one measurable lesion of ≥ 1 cm or a non-measurable assessable lesion, adequate bone marrow, liver, and renal function, WHO performance status 0 to 2, age 18 to 80 years, and no previous chemotherapy for metastatic disease. Previous adjuvant chemotherapy was required to have been completed at least 6 months before inclusion. Patients from the control arm received FOLFOX4, while those from the investigational arm were given six cycles of FOLFOX7, followed by 12 cycles of the simplified leucovorin + fluorouracil regimen (2-hour infusion of leucovorin isomers, l-LV 200 mg/m^2 or dl-LV 400 mg/m^2, followed by fluorouracil: 400 mg/m^2 bolus and 46-hour 3000 mg/m^2 infusion every 2 weeks), and finally, six additional cycles of FOLFOX7. Treatment in both arms was continued until progression, unacceptable toxicity, or patient choice. A total of 620 patients who met the inclusion criteria were randomly assigned to the control arm (n = 311) or to the investigational arm (n = 309). The median progression-free survival was 9.0 months in the control arm compared with 8.7 months in the investigational arm (HR = 1.06; 95% CI: 0.89–1.20; p = 0.47). Median survival time was 19.3 months in patients allocated to the control arm compared with 21.2 months in patients allocated to the investigational arm (HR = 0.93; 95% CI: 0.72–1.11; p = 0.49). The tumor response rates did not differ significantly between the two treatment arms (control arm: 58.5%; 95% CI: 54.5–62.5%; investigational arm: 59.2%; 95% CI: 55.2–63.2%) as well. Initially, the tolerability and toxicity profiles of the two regimens were similar: overall, 54.4% and 48.2% of patients experienced grade 3 or 4 toxicity in the control and investigational arm, respectively. However, the risk of developing grade 3 to 4 toxicity was greatly reduced in the investigational arm from cycle 7 to cycle 18, when patients did not receive oxaliplatin [32]. This study showed that periodic discontinuation of oxaliplatin markedly reduces the toxicity of the FOLFOX protocol, at no expense of the therapeutic outcomes.

Conclusions

The hereby presented analysis of randomized trials did not identify unambiguously an optimal duration of first-line chemotherapy in patients with disseminated colorectal cancer. None of the studies proved the superiority of 12 cycles of the FOLFOX or FOLFIRI regimen, being the most commonly used standard in this setting. Although longer duration of this treatment may be associated with higher response rates and longer progression-free survival, these improvements frequently prove insignificant on statistical analyses. Noticeably, the prolonged treatment has no significant effect on overall survival. Moreover, longer duration of treatment is undoubtedly associated with greater toxicity. Furthermore, there is no evidence that treatment shorter than 12 cycles, administered every second week, has a negative impact on overall survival. Nevertheless, selected subpopulations of patients could probably benefit from the shorter treatment.

The options of intermittent chemotherapy with periodic elimination of the most toxic agents seem particularly interesting. The use of this strategy was associated with marked decrease in the prevalence of grade 3 and 4 toxicities. Also the strategy of scheduled chemotherapy holidays seems advisable, as it is associated with similar efficacy as continuous treatment but lower toxicity.

Due to increasing popularity of targeted therapies, either as the first-line treatment of disseminated colorectal cancer in highly developed countries or as a subject of clinical trials, obtaining an unequivocal answer to our introductory question is unlikely. However, this question should not be neglected, as still the majority of individuals from developing countries received conventional chemotherapy in a palliative setting. The hereby reviewed sparse literature data suggest that palliative chemotherapy of disseminated colorectal cancer should be planned on an individual basis, and preferences of a given patient, informed about both potential clinical benefits and side effects of all available therapeutic strategies, should be taken into account. In cases free from progression or inacceptable toxicity, total duration of the first-line treatment and its intensity should represent a compromise between evidence-based medical knowledge and patient's preferences.

The authors declare no conflict of interest.

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Submitted: 10.06.2014
Accepted: 20.08.2014