

How long to treat metastatic colorectal cancer?

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The natural history of metastatic colorectal cancer (mCRC) has dramatically evolved in the recent years thanks to the introduction of modern chemotherapy. Today, with the new drugs such as oxaliplatin and irinotecan, and modern drugs based in molecular targets (bevacizumab and cetuximab), the response rate has increased to 50%, the progression free survival to 12 months and overall survival is longer than 2 years.

In spite of this progress, many questions remain to be answered, especially those related to the sequential regimes, alternant and intermittent schedules, drug rotation, reintroduction of the same regimes or drugs, optimal duration of chemotherapy, and the role of maintenance chemotherapy (1,2).

Optimal duration of chemotherapy is crucial, because it has a direct influence on quality of life, toxicity and cost; as well as its potential relationship with survival. To perform an induction chemotherapy (3-6 months of treatment) and then to stop until disease progression, or even to include chemotherapy holidays, is a very attractive and extensive practice among oncologists, although not very well validated. This approach could only be considered reasonable when progression free survival (PFS) and overall survival (OS) are not compromised. In any case it is necessary to keep in mind that the objective of the chemotherapy is palliative and the potential toxicity of the drugs in some cases, cumulative. Of course, in those cases in which the disease is limited but metastasis are unresectable at front, the objective is tumor shrinkage in order to achieve a response that could allow a resectability of the metastasis. Consequently, the strategy is to use the best chemotherapy regime (doublets + biologic agent). Nevertheless in more than 80% of the cases chemotherapy will be palliative.

In palliative settings, for practical decisions, there are two different groups of patients: 1) those with tumor-related symptoms in which the objective is tumor shrinkage in order to obtain a rapid response for the control of the symptoms and for which the strategy is to use the best chemotherapy regime; and 2) those with only mild symptoms, in which the objective is survival and quality of life. In the latter, the strategy is to use the "continuum of care". According to Grothey (1) "continuum of care" means to use distinct lines of therapy with two goals: employ all potential active agents and prevention and management of toxicities. In this context duration and intensity of therapy are of great importance.

Different strategies have been used to answer the question about optimal duration of chemotherapy in the palliative setting. The main goal in the majority of the studies is to use an induction chemotherapy for several months followed by free-intervals of chemotherapy (chemo-holidays) of all agents or only some of them. To summarize, the three approaches are: 1) "Stop and go" strategy: stopping all chemotherapy agents after a pre-fixed number of cycles and restart on progression, 2) intermittent administration of chemotherapy (on-off strategy) and 3) maintenance chemotherapy stopping only some agents.

Stop and Go

Three studies have analyzed this strategy: MRCC trial (2), the Optimox 2 (3) and the more recent MRC-COIN study (4).

The MRCC trial (2) recruited 354 patients from 42 UK centers. After receiving chemotherapy in first line for 12 weeks (DeGramont, Lokich or raltitrexed), the patients were distributed to continue the therapy or to stop and reintroduce it at the progression. Although PFS and OS were slightly superior in the continuous arm, the difference was not statistically significant and toxicity was lower in the patients with the intermittent treatment. These findings provide no clear evidence of a benefit in continuing therapy indefinitely until disease progression, however the regimes used did not include modern drugs like oxaliplatin and irinotecan.

The Optimox 2 study (3) compares chemotherapy discontinuation with maintenance therapy with leucovorin and fluorouracil after six cycles of folinic acid, fluorouracil and oxaliplatin

(FOLFOX). Duration of disease control (DCC) which was the main objective of the study was inferior in the discontinuation arm (9.2 m vs 13.1 m). PFS was also inferior as well (6.6 m vs 8.6 m). The authors concluded that the planned discontinuation of the chemotherapy had a negative impact compared with the maintenance therapy strategy.

MRC COIN (4) study compared in a large population (1630 patients) whether intermittent chemotherapy with oxaliplatin + fluoropyrimidine (OxFp) was non-inferior to standard continuous OxFp in terms of OS. In the ITT analysis OS was 14.3 m vs 15.6 m and in the per protocol 17.6 m vs 19.1 m. The author concluded that a priori specified non-inferiority cannot be confirmed, but it can reliably exclude a detriment of larger than 2.3 m in median survival with intermittent CT.

Intermittent (on-off strategy)

In a randomized study with 336 patients, the Italian GISCAD (5) group compared the administration of the continuous FOLFIRI regime versus the intermittent FOLFIRI regime (alternating 2 months on and 2 months off). The results showed the same OS (17.6 m vs 16.9 m) and PFS (7.3 m vs 8.8 m) in both arms and a reduction in discomfort and economic costs.

Maintenance strategy (stopping only some agents)

OPTIMOX1 is a randomized study of the GERCOR group (6) comparing in 620 patients the administration of FOLFOX4 until disease progression or FOLFOX7 (a simpler regime with a higher dose of oxaliplatin) for three months and then stopping the administration of oxaliplatin for 6 months and finally a reintroduction of FOLFOX7. There were not any significant differences in the response rate (58.5% vs. 59.2%), in the PFS (9 months vs. 8.7 months) or in the OS (19.3 months vs. 21.2 months). The reintroduction of oxaliplatin was performed in 40% of patients. This study showed that oxaliplatin treatment could be stopped without compromising the results ("stop and go" strategy). The hematological toxicity (neutropenia grade 3/4) and the neurotoxicity grade 3 were lower, favoring FOLFOX7 with the exception of thrombopenia.

The CONcePT (7) is an American trial comparing the administration of intermittent oxaliplatin vs continuous oxaliplatin in the FOLFOX plus bevacizumab regimen. Time to treatment failure and PFS were inferior in the continuous administration (5.6 vs 4.2 m and 12 vs 6.6 m).

MACRO-TTD trial (8), is a Spanish multicenter, randomized, phase III study aimed to evaluate in 480 pts, the efficacy and tolerability of 6 cycles of BEV + XELOX (capecitabine + oxaliplatin) followed by maintenance of XELOX-BEV or single/agent BEV. There were not statistically significant differences between the two arms in ORR (62% vs 59%), PFS (10.3 m vs 9.7 m) and OS (23.4 m vs 21.6 m). G3-G4 toxicities were inferior in the maintenance arm concerning hand-foot syndrome, asthenia and neuropathy. This study suggests that maintenance therapy with single/agent BEV is an appropriate option following the induction XELOX-BEV in pts with mCRC.

Practical recommendations for mCCR:

These studies reinforce the frequent behavior of the oncologist to stop the treatment when they understand that the patient has obtained the maximum response. Nevertheless some methodological problems in the analyzed trials have determined that not all the oncologists agree with this proposal, consequently it has been quite difficult to consent on a generalized message. In this situation it seems essential to perform well designed clinical trials incorporating the new drugs like bevacizumab and cetuximab, and analyzing not only the optimal duration of chemotherapy but also the role of maintenance.

The practical recommendations that could be proposed must be performed only in cases in which the disease is non-resectable, and not potentially curable which means that this proposal is only for palliative treatment. In this situation the goal is to obtain a response rate in 50% of the patients, a PFS of about 9-10 months and an OS of around 20 months. Of course quality of life is essential, and for these patients the possibilities are the following:

1. Classical way: This is the standard and consists of the administration of chemotherapy indefinitely until disease progression, unless there is unacceptable toxicity or the patient decides to end the treatment. After progression a second line of chemotherapy will be offered.

2. The alternative is to administer chemotherapy, in first line, for a limited number of cycles or until the maximum response is obtained. The length of chemotherapy could be around 3-6 months. After this stage, there is type IIB evidence that suggests to use of mono-chemotherapy alone (OPTIMOX 1 study) or plus bevacizumab (CONcePT study) or bevacizumab alone (MACRO study) as a maintenance. The detrimental effect on the OS could be around 6-8 weeks but on the contrary this strategy reduces the cost, increase quality of life, allow to receive more lines of chemotherapy and prevent discontinuation of treatment. The decision should be based on an individual approach and taking into account all the clinical parameters. As opposed to the "stop and go strategy" (MRC, OPTIMOX 2 and COIN trials), when controversial data is considered, (even negative data), we do not recommend complete breaks of CT. When the disease progression is confirmed it would be possible to reintroduce the same chemotherapy regimen used in first line or to pass to a second line regimen of chemotherapy.

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