Critical Reviews in Oncology / Hematology 131 (2018) 53–65

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Duration of first-line treatment for metastatic colorectal cancer: Translating the available evidence into general recommendations for routine practice

Federica Morano[a], Francesco Sclafani[b,*]

[a] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[b] The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom

ARTICLE INFO

Keywords:
Metastatic colorectal cancer
First-line chemotherapy
Duration of treatment
Maintenance treatment
De-escalated treatment
Cetuximab
Bevacizumab

ABSTRACT

Over the last two decades the number of front-line regimens for metastatic colorectal cancer has progressively increased. Nevertheless, there is still no consensus on the optimal duration of treatment or the role of de-escalated/maintenance strategies after induction chemotherapy. In this article we provide an overview of the studies that addressed the duration of first-line systemic treatment with cytotoxic agents plus or minus targeted therapies highlighting caveats and limitations of the same. Also, we try to translate the available evidence into practical recommendations that can be used in everyday practice to inform treatment decisions. The main conclusion of our review article is that continuing induction treatment until progression may improve disease control but there is no evidence to suggest that adopting this practice can prolong survival. On the other hand, de-escalated treatment strategies offer an opportunity to reduce the burden of toxicity while maintaining satisfactory oncological outcomes.

1. Introduction

In 2012 colorectal cancer (CRC) was the third most common cancer in men and the second in women globally with 1.4 million new cases diagnosed and 693,900 deaths (Torre et al., 2016). Approximately 20% of CRC patients present with metastatic disease at diagnosis and a further 20–25% will develop metastases during the course of the disease (Shah et al., 2016; Cancer Research UK, 2018). Only a minority of patients with metastatic (m)CRC are suitable for a potentially curative approach, most of them being candidates for palliative treatments that aim to reduce or delay tumour-related symptoms and prolong survival (Folprecht et al., 2005). In this setting, keeping treatment-related toxicities to a minimum and preserving quality of life (QoL) and functioning are paramount for patients and healthcare providers.

The concept of finding a good balance between efficacy and toxicity of treatments for unresectable mCRC largely inspired clinical research during the past decades. A number of trials were conducted which showed that management strategies based on the sequential administration of cytotoxic agents were non-inferior, at least in terms of overall survival (OS), compared with more aggressive approaches including upfront combination chemotherapy regimens (Seymour et al., 2007; Koopman et al., 2007; Cunningham et al., 2009; Ducreux et al., 2011; Seymour et al., 2011). Also, studies of intermittent or de-escalated first-line treatment strategies overall supported the contention that satisfactory long-term outcomes can be achieved while reducing exposure to cytotoxic agents and toxicity (Maughan et al., 2003; Tournigand et al., 2006; Chibaudel et al., 2009; Adams et al., 2011; Labianca et al., 2011).

There is no doubt, however, that since these pivotal studies were designed, the therapeutic landscape of mCRC has progressively changed. The increased number of cytotoxic agents, advent of targeted therapies and frequent use of surgical/organ-directed treatments have expanded the available therapeutic options and substantially improved life expectancy (Hurwitz et al., 2004; Saltz et al., 2008; Van Cutsem et al., 2009; Douillard et al., 2010; Loupakis et al., 2014; Van Cutsem et al., 2012; Bennouna et al., 2013; Tabernero et al., 2015; Grothey et al., 2013; Mayer et al., 2015; Glehen et al., 2003). Trials with doublet or triplet chemotherapy regimens plus targeted therapies have reported median OS of up to 30 months, these results challenging the historical assumption that a less intensive, sequential therapy strategy is non-inferior to a more aggressive, upfront combination treatment approach. Furthermore, a better understanding of the tumour biology and the identification of predictive/prognostic factors have provided oncologists with valuable tools to guide treatment decisions and improve the risk/benefit ratio of therapeutic interventions in selected groups (Douillard et al., 2013; Heinemann et al., 2014; Venderbosch et al., 2014; Van Cutsem et al., 2015; Arnold et al., 2017).

Therefore, although QoL still remains a priority in the management

* Corresponding author at: Department of Medicine, The Royal Marsden NHS Foundation Trust Hospital, Sutton, Surrey, SM2 5PT, United Kingdom.
E-mail address: francesco.sclafani@rmh.nhs.uk (F. Sclafani).

https://doi.org/10.1016/j.critrevonc.2018.08.006
Received 16 January 2018; Received in revised form 22 July 2018; Accepted 22 August 2018
1040-8428/

of mCRC patients with incurable disease, there has been a renewed interest in the investigation of the optimal intensity and duration of first-line treatment. This has been especially prompted by the availability of targeted therapies such as anti-EGFR and anti-VEGF monoclonal antibodies that can, not only build on the efficacy of standard chemotherapy with limited incremental toxicity, but also allow the use of continuous treatment schedules that are better tolerated, less detrimental to QoL and therefore more acceptable compared with those based on cytotoxic agents. More recently, the therapeutic potential of novel treatment options including immunotherapy has led investigators to test alternative maintenance strategies following completion of standard chemotherapy.

Several randomised trials have addressed the optimal duration of first line-treatment. Proposed treatment approaches can be summarised as follows: 1) "stop-and-go strategy" (*i.e.*, all drugs stopped and re-started upon tumour progression); 2) "on-off strategy" (*i.e.*, treatment administered intermittently at pre-defined intervals); 3) "maintenance strategy" (*i.e.*, de-escalated treatment continued until tumour progression). The aim of this article is to review the available evidence on the optimal duration of first-line systemic treatment for mCRC as emerged in the era of cytotoxic agents and after the introduction of targeted therapies and to translate this into general recommendations for everyday's clinical practice. Ongoing clinical trials investigating this topic are also presented.

2. Duration of first-line treatment in the chemotherapy era

The first trial was conducted by the Medical Research Council (MRC) in the UK (CR06B) (Maughan et al., 2003). The primary aim was to demonstrate that continuing treatment until disease progression, unacceptable toxicity or patient choice was superior in terms of OS compared to stopping treatment after 12 weeks and re-starting the same upon tumour progression. In this study which closed prematurely due to slow accrual, 354 patients who had achieved stable disease (59%) or objective response (41%) after fluorouracil (5-FU) and folinic acid (LV), continuous intravenous infusion 5-FU or raltitrexed were enrolled. Despite the study recommendations, only 37.1% of patients in the intermittent treatment group were successfully re-challenged while second-line chemotherapy was received by 34.8% and 30.1% of patients in the intermittent and continuous treatment group, respectively. Median, 1-year and 2-year OS was 10.8 months, 46% and 19% in the intermittent and 11.3 months, 45% and 13% in the continuous treatment group, respectively (HR 0.87 [favouring intermittent], p = 0.23). No statistically significant difference in progression-free survival (PFS) was observed (HR 1.20 [favouring continuous] p = 0.10). Treatment-related adverse events did not differ between the two arms with the only exception of rash (more frequent in the continuous treatment group). Interestingly, continuing treatment until progressive disease did not appear to be associated with a detrimental effect on QoL (Table 1).

In the OPTIMOX-1 trial, Tournigand and colleagues investigated whether discontinuation and subsequent reintroduction of dose-intense oxaliplatin was superior to standard continuous chemotherapy and could reduce cumulative sensory peripheral neuropathy (Tournigand et al., 2006). Patients were randomly allocated to receive either continuous FOLFOX-4 until disease progression or unacceptable toxicity or 6 cycles of FOLFOX-7 followed by 12 cycles of simplified LV5FU2 and 6 further cycles of FOLFOX-7 (n = 620). The primary endpoint was duration of disease control (DDC) (*i.e.* PFS or sum of the initial PFS and the PFS after oxaliplatin reintroduction if no progression at the first assessment). The use of second-line therapies in both treatment arms was substantially higher (> 70%) compared to the MRC trial but oxaliplatin was again reintroduced in only 40.1% of patients in the de-escalation arm. No statistically significant difference between treatment groups was observed in terms of DDC (9 months in the FOLFOX-4 arm *vs* 10.6 months in the FOLFOX-7 arm, HR 0.99, p = 0.89) and OS (19.3 months in the FOLFOX-4 arm *vs* 21.2 months in the FOLFOX-7 arm, HR 0.93, p = 0.49). Toxicity was also comparable overall with the exception of a reduced risk of grade ≥3 events during the pre-defined break from oxaliplatin. Although the median oxaliplatin dose-intensity was higher in the de-escalation arm, a trend towards a reduced incidence of grade 3 sensory neuropathy in this treatment group was observed (13.3% *vs* 17.9%, p = 0.12). Of note, in a subsequent post-hoc analysis, the reintroduction of oxaliplatin in individual patients as well as the reintroduction rate in participating centres was associated with improved OS (de Gramont et al., 2007).

Further to these results, a randomised phase III trial (OPTIMOX-2) was designed to demonstrate that a strategy of 12-week induction mFOLFOX-7 followed by a chemotherapy-free interval and treatment reintroduction upon tumour progression was superior to the investigational arm of the OPTIMOX-1 trial (de-escalated mFOLFOX-7) (Chibaudel et al., 2009). This study suffered from poor accrual which resulted in a relatively small sample size (n = 202) and lack of a pre-defined statistical hypothesis (Chibaudel et al., 2009). The primary endpoint was DDC as previously defined in the OPTIMOX-1 study. This was statistically significantly longer in the continuous compared with the intermittent treatment group (13.1 *vs* 9.2 months; HR 0.71, p = 0.046). A numerically better median OS was also reported in favour of the continuous treatment arm (23.8 *vs* 19.5 months, HR 0.88, p = 0.42). Of note, in this study the oxaliplatin reintroduction rate (55.1% in the continuous and 63.5% in the intermittent arm) was higher compared to the OPTIMOX-1 trial. No major differences in toxicity were observed when the induction and reintroduction treatment periods were compared between the two study arms. Similarly to the OPTIMOX-1 study, QoL was not assessed.

The MRC COIN trial was the largest study to investigate intermittent first-line chemotherapy in mCRC (Adams et al., 2011). In this non-inferiority phase III trial (primary endpoint OS) patients were randomly assigned to continuous treatment with a fluoropyrimidine and oxaliplatin until progressive disease/unacceptable toxicity or the same regimen administered intermittently (*i.e.*, 12 weeks induction period followed by observation and treatment reintroduction upon tumour progression). The median OS in the intention-to-treat (ITT) population (n = 1630) was 15.8 months for the continuous and 14.4 months for the intermittent treatment arm (HR 1.084). In the per-protocol population (n = 978) these figures were 19.6 months and 18.0 months, respectively (HR 1.087). The study failed to demonstrate that intermittent treatment was non-inferior to the continuous treatment as the upper limit of the 80% confidence interval for the survival estimate in both the ITT (HR 1.165) and per-protocol population (HR 1.198) was higher than the pre-defined non-inferiority boundary (HR 1.162). The rate of chemotherapy reintroduction in the intermittent arm was 39.9% and 63.6% among the ITT and per-protocol population, respectively. Interestingly, in a pre-defined subgroup analysis of the per-protocol population, the intermittent treatment strategy appeared to be detrimental to OS in patients with a high platelet count at baseline (p = 0.0027). A similar trend was observed in those with liver-only metastases (p = 0.066) and *KRAS* wild-type tumours (p = 0.070). The analysis of toxicity experienced after 12 weeks in the per-protocol population showed that the rate of grade ≥3 adverse events was higher for nausea (7% *vs* 2%), vomiting (4% *vs* 2%), anorexia (5% *vs* 3%) and pain (16% *vs* 9%) in the intermittent compared with the continuous treatment group but lower for neutropenia (12% *vs* 8%) and peripheral neuropathy (27% *vs* 5%). QoL was analysed in a subset of the per-protocol population and, although no difference in global health status was found between the two treatment arms, numerous functional and symptom scales/items were better while pain was worse for the intermittent treatment group.

More recently, Luo et al assessed the safety and efficacy of maintenance treatment with single agent capecitabine in 274 Chinese patients who had achieved at least stable disease after 18–24 weeks of oxaliplatin-based chemotherapy (Luo et al., 2016). The primary endpoint of this phase III study was PFS. Median PFS in the maintenance