Cancer Treatment Reviews 42 (2016) 82–90

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Maintenance strategy in metastatic colorectal cancer: A systematic review

Ece Esin [1,2], Suayib Yalcin [*,1]

Hacettepe University Cancer Institute, Department of Medical Oncology, Sihhiye, 06100 Ankara, Turkey

ARTICLE INFO

Article history:
Received 9 May 2015
Received in revised form 22 September 2015
Accepted 30 October 2015

Keywords:
Maintenance
Colorectal carcinoma
STOP and GO
Chemotherapy free interval
Drug holiday

ABSTRACT

Purpose: Colorectal cancer is the third most common cancer in men and second in women, estimated to cause 694,000 deaths worldwide in 2012. Although 5-year survival rate of CRC has increased, inoperable metastatic colorectal cancer (mCRC) is almost always fatal. The aim of this systematic review is to outline the maintenance strategies that increase the chance and duration of survival with less toxicity and sustained quality of life.

Design: Literature search in PubMed, in American Society of Clinical Oncology (ASCO) Annual Meetings and in ASCO Gastrointestinal Symposia and European Society for Medical Oncology (ESMO) Congresses was performed. Studies conducted in adult patients were written in English language and were published in peer-reviewed journals as phase II or III randomized controlled trials (RCTs) comparing continuous chemotherapy to intermittent chemotherapy, each with or without maintenance therapy was included along with at least one of the outcomes of interest.

Results: Twenty randomized controlled trials and systematic reviews were included from Medline search, together with 4 abstracts from ASCO meetings and 2 abstracts from ESMO meetings.

Conclusion: Existing evidence-based data show that prolonged progression free survival (PFS) can be achieved with less toxic regimens compared to complete drug holidays or continued treatment. However, the impact of maintenance on overall survival is less clear. The specific data for maintenance with biological agents are evolving, while in general fluoropyrimidine based maintenance with bevacizumab is better than Bev alone or observation for PFS. Data regarding Cetuximab maintenance are less pronounced than that of Bev maintenance. Preliminary data show that erlotinib-Bev combination may be of benefit as maintenance. Although maintenance may provide significant clinical benefit in clinical studies, the optimal strategy should still be individualized.

Introduction

Colorectal cancer (CRC) is among the leading malignancies in terms of incidence and mortality worldwide. According to the 2014 World Cancer Report, it is the third most common cancer in men and second in women, estimated to cause 694,000 deaths in 2012 globally [1]. Although the 5-year survival rates of CRC is increased from 51% to 65% and more patients are diagnosed at earlier stages, half of the CRC patients will eventually develop metastasis, inoperable metastatic colorectal cancer (mCRC) is almost always fatal [2]. The increase in the number of long term survivors, considered with the burden of incurable mCRC patients emphasize the importance of palliative treatment and quality of life (QOL) and raise the question of how to achieve the optimal treatment strategy and duration.

The most active regimens used in CRC are based on fluoropyrimidines used in combination with oxaliplatin or irinotecan and with or without targeted agents such as bevacizumab, cetuximab (Cet) or panitumumab. The median overall survival (OS) of CRC patients now exceeds 33 months in phase 3 studies [3–5]. As the OS of CRC is increased, expected and exposed toxicities of the chemotherapy are also increased. In clinical practice, one of the major dose-limiting toxicity of oxaliplatin is the peripheral sensory neuropathy. Neuropathy is cumulative but usually regressive to some degree after drug discontinuation but maybe disabling [6]. Irinotecan is generally tolerated better and has less clinically relevant cumulative toxicity. Therefore, strategies to diminish the toxicity of treatments, to increase the QOL and to develop optimal strategies for longer survival are a major concern of investigators especially in patients receiving oxaliplatin based regimens, making

* Corresponding author. Tel.: +90 312 305 2929; fax: +90 312 305 2905.
E-mail address: suayibyalcin@gmail.com (S. Yalcin).
[1] Ece Esin and Suayib Yalcin have equally contributed to this work.
[2] Tel.: +90 312 305 2929; fax: +90 312 305 2905.

http://dx.doi.org/10.1016/j.ctrv.2015.10.012
0305-7372/

maintenance strategies as one of the key issues in the management of mCRC.

This review will summarize the randomized controlled trials (RCTs), which include maintenance strategy in mCRC.

Methods

Search strategy and study identification

Literature searches in PubMed (1990 to March 2015), American Society of Clinical Oncology (ASCO) Annual Meetings (1997–2014), ASCO Gastrointestinal Symposia (GI) (2000 to 2014), and European Society for Medical Oncology (ESMO) Congresses (2000 to 2014) were performed. The selection and the writing process were completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [7]. The main keywords used for the search were ^maintenance^ and ^colon cancer^ or ^rectal cancer^ or ^colorectal cancer^. In order to increase the sensitivity of search results, reference lists of the retrieved articles were manually screened and necessary citations were included into the systematic review.

Studies conducted in adult patients were written in English-language, were published in peer-reviewed journals as phase II or III randomized controlled trials (RCTs) comparing continuous chemotherapy to an intermittent strategy of chemotherapy, with or without maintenance therapy included at least one of the outcomes of interest were included. The ASCO, ESMO and the ASCO GI meeting abstracts as well as the systematic reviews and meta-analyses were also accepted for inclusion.

Literature search results

The Medline search yielded 1056 hits, of which 47 were potentially relevant and were fully reviewed, and 20 of these were retained. Twelve abstracts from the ASCO meetings were retrieved and 4 of these were retained. Two ESMO meeting abstracts were also included. In Table 1, the study selection process is outlined.

What is maintenance?

Relatively few patients can tolerate full doses of chemotherapy for periods longer than 4–6 months. A number of RCTs have investigated the strategies of optimal palliative treatment in mCRC. The main point was the prevention of time related cumulative toxicities (neuropathy, asthenia, diminished psychological well-being and liver injury) of treatment with maximum benefit. Continuous strategy involves non-stop application of induction treatment until disease progression or until the development of unacceptable toxicity (Fig. 1). Intermittent treatment is the strategy that involves an induction period using chemotherapy with or without a targeted agent (Bev, Cet or Pan) followed by a drug discontinuation period, termed "drug holiday" (Chemotherapy free interval, Fig. 2) or continuation with some drugs of induction (de-escalation, generally oxaliplatin or rarely irinotecan), termed "maintenance" (Fig. 3). After predefined disease progression or preplanned duration of holiday or maintenance, re-induction is usually applied.

How to maintain the treatment? – With/without chemotherapy

Maintenance chemotherapy is designed to control the tumor growth with less intensive and toxic regimen while preserving more efficient but toxic strategy to disease progression. There are several ways for applying induction therapy and maintenance following it. The clinical trials of induction with chemotherapy only maintenance will be outlined here.

Most of the maintenance trials utilize FOLFOX or XELOX (CapeOx) for induction. Intermittent strategy was challenged earlier in a Medical Research Council study [10]. Patients who were stabilized or who achieved partial response after 12 week of initial treatment were randomized to continuous arm or drug holiday. In disease progression, resumption of the initial regimen was applied to patients in chemotherapy free arm. Re-induction of the initial regimen was generally offered to the patients by their primary physicians at the time of progression, but it was not mandatory. The primary endpoint was OS. Median survival was in favor of continuous arm but it was not statistically significant (10.8 months vs. 11.3 months, HR: 0.87: 95% CI: 0.69–1.09, $p = 0.23$). Continuous strategy resulted in 1-month delay in progression but it was not statistically significant (3.7 vs. 4.9 months, HR: 1.20; 95% CI: 0.96–1.49, $p = 0.10$). Patients on intermittent arm reported less CTX-related side effects but their overall health and physical functioning reports were similar. The pitfall of the MRC trial was that a significant number of patients refused randomization and unplanned re-induction upon progression, but gave some clue that stopping treatment may not be a good option. In OPTIMOX-1 trial, continuous FOLFOX-4 regimen was compared with intermittent FOLFOX-7 regimen with fluorouracil-folinic acid (FUFA) maintenance in interval period [11]. There was no significant difference in terms of disease control duration (DDC, in maintenance arm 10.6 months), progression free survival (PFS, in maintenance arm 8.7 months) or OS (21.2 months in maintenance arm). Discontinuation of oxaliplatin until disease progression did not yield inferior results when a fluoropyrimidine maintenance was provided, and patients remained sensitive to oxaliplatin, which is important for the success of the re-induction regimen. OPTIMOX-2 trial was designed to give a total chemotherapy holiday to minimize the increased toxicity of FOLFOX-4 regimen as a confounding factor [12]. As a second arm, a chemotherapy-free interval was applied to a group of patients. The regimen in OPTIMOX-2 study included a lower dose-intense oxaliplatin with an increase in the dose of 5-FU without a bolus in order to decrease the incidence of hematologic toxicity. During the progression or as disease got symptomatic; re-introduction of chemotherapy was planned. The primary end point was defined as the duration of disease control (DDC). In the case of FOLFOX7 reintroduction and success, DDC was defined as the sum of first and second progression-free interval. If FOLFOX7 failed for the second round, then only PFI of first chemotherapy round was applied. These rules were originally applied for both maintenance and CFI arms. The primary endpoint, DDC, was longer in the maintenance arm compared to the CFI arm (13.1 months vs. 9.2 months, HR: 0.71, 95% CI, 0.51–0.99, $p = 0.046$). Maintenance therapy increased the PFS from 6.6 months to 8.6 months (HR = 0.61; $p = 0.0017$). In comparison to OPTIMOX-1 trial (21.2 months), median survival of the maintenance arm was increased to 23.8 months. Median survival was increased to 23.8 months in maintenance arm; however, it was not statistically significant (HR: 0.88, $p = 0.42$). The results of both trials support the use of discontinuation of oxaliplatin and the use of maintenance with FUFA regimens [11,12]. On the contrary, based on the results of OPTIMOX-2, CFI was not shown to be safe. Of note, OPTIMOX-2 was a phase II trial and the first induction of FOLFOX was applied only for 6 cycles (3 months), which could be considered as suboptimal in the light of the current available data for mCRC treatment.

The COIN trial investigators also assessed the effect of drug holiday in mCRC [13]. This trial had three arms: Arm-A patients were introduced with continuous CTX (FU/Capecitabine with oxaliplatin), arm-B patients received continuous CTX with Bev, and arm-C patients were off the drug until the disease progression after 12 weeks of induction chemotherapy. The primary objective, non-inferiority of intermittent therapy, in terms of OS could not be