Cancer Letters 400 (2017) 319–324

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Metronomic chemotherapy in metastatic colorectal cancer

In Sook Woo*, Yun Hwa Jung

Division of Medical Oncology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul, 07345, Republic of Korea

ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form
26 February 2017
Accepted 27 February 2017

Keywords:
Low dose
Metronomic chemotherapy
Metastatic colorectal cancer

ABSTRACT

Overall survival and quality of life of patients with metastatic colorectal cancer (mCRC) have improved due to the development of standard systemic treatment. However, many patients are still suffering from the eventual progression of cancer, treatment-related toxicities, and the economic burden of new drugs. Salvage or maintenance therapy, which consistently controls or stabilizes tumor progression without debilitating quality of life, is required. Recently, metronomic capecitabine maintenance therapy after disease control using conventional chemotherapy with maximal tolerated doses has demonstrated beneficial results in a phase III trial. Metronomic chemotherapy has been known to control tumors through antiangiogenesis and immunomodulation as well as a direct effect on tumor-initiating cells. It has the characteristics of being minimally toxic, inexpensive, and durable for maintaining disease stabilization. Therefore, patients with mCRC, who tend to be elderly and frail and have been previously treated, might be suitable for metronomic therapeutic strategies. Furthermore, antiangiogenic therapy has been an important component in treating mCRC, but the schedules and doses of metronomic chemotherapy have not yet been established. Here we review translational and clinical research on metronomic chemotherapy in colorectal cancer (CRC).

Introduction

Colorectal cancer (CRC) is one of the most common cancers and a major cause of death worldwide [1,2]. Approximately 20% of CRC has already reached distant metastasis at the time of diagnosis, and the 5-year survival rate of metastatic colorectal cancer (mCRC) ranged from only 5.5% to 12.5% from 1975 to 2009, according to recent data [2]. Overall survival of patients with mCRC has been prolonged by multiple lines of systemic treatment; however, the disease still has a poor prognosis despite advances in chemotherapy and biologic agents. Salvage options are still lacking for mCRC after conventional protocols. Patients' performance and quality of life may worsen with repeated conventional cytotoxic chemotherapy. Additionally, 24% of new patients with CRC are 80 years and older [2], and these elderly patients are fragile, tend to present with comorbid illnesses, and can be reluctant to undergo systemic chemotherapy due to treatment-related toxicities and economic difficulties. Without systemic treatment, both heavily pretreated and vulnerable elderly patients with mCRC might lose opportunities for palliation following reductions in their tumor burdens; therefore, systemic therapy that does not worsen quality of life but effectively controls the disease is necessary for this population. Metronomic chemotherapy refers to either constant (daily, multiple times a week, or weekly) or continuous administration of low-dose cytotoxic drugs administered without extended interruption; the drugs used were usually inexpensive oral chemotherapeutic agents. Metronomic chemotherapy was once thought to reduce tumor burden mainly through antiangiogenic mechanisms rather than cytotoxic effects [3,4]. Later, it was revealed to act not only on tumor vasculature but also on the immune system and, directly, on cancer cells; it showed clinical efficacy with a lower toxicity profile than maximum tolerated dose (MTD) chemotherapy [4,5]. Even the same chemotherapeutic agents that were previously used in MTD chemotherapy showed efficacy when administered again through the metronomic method.

Phase I and II studies of metronomic chemotherapy for solid tumors have been reported for metastatic breast cancer, non-small cell lung cancer, glioblastoma, and CRC [6–10]. However, the most recent pharmacokinetic studies on metronomic chemotherapy have reported, in humans in vivo and in vitro, on clinical biomarkers and types of drugs but have not clearly defined optimal doses and schedules for anticancer drugs.

Abbreviations: CRC, colorectal cancer; mCRC, metastatic colorectal cancer; MTD, maximal tolerated dose; PFS, progression-free survival; OS, overall survival; TSP-1, thrombospondin-1.

* Corresponding author. Fax: +82 2 780 3132.
E-mail address: insookwoo@catholic.ac.kr (I.S. Woo).

http://dx.doi.org/10.1016/j.canlet.2017.02.034
0304-3835/

Antiangiogenic treatment has been approved for mCRC through a phase III study since 2004 [11], and metronomic chemotherapy based on inhibiting angiogenesis could be an effective therapeutic option for mCRC. Recently, a phase III study of metronomic capecitabine combined with bevacizumab as maintenance chemotherapy in mCRC demonstrated better progression-free survival (PFS) compared to the observation group after inducing stable disease or objective response with standard MTD chemotherapy [12]. Less toxic, well-tolerated regimens may allow for sustained disease control similar to that with chronic diseases. In the era of precision medicine, clinical trials of metronomic chemotherapy in combination with targeted agents or repositioning of other drugs are needed.

Here we review preclinical and clinical studies on metronomic chemotherapy in CRC.

Development of systemic treatment for mCRC

Fluorouracil has been the backbone of chemotherapy in CRC. In patients with advanced CRC, continuous infusion of fluorouracil (5-FU) showed a higher overall response rate (22% vs. 14%, $P = 0.0002$) and longer overall survival (OS) than did a bolus administration, and grade 3 and 4 hematologic toxicities were lower in the continuous infusion group (4% vs. 31%) [13]. 5-Fluorouracil/leucovorin (5-FU/LV) had been the standard therapy for mCRC patients until 2004, with an estimated median OS of 10–14 months [14]. Oral capecitabine, a fluoropyrimidine prodrug, is activated to 5-FU by intracellular thymidine phosphorylase within tumor cells and does not require intravascular devices or pumps [15]. In a phase III randomized trial that compared oral capecitabine and intravenous fluorouracil plus leucovorin as a first-line mCRC treatment, oral capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by 1 week of rest) showed a superior response rate to that of 5-FU/LV (24.8% and 15.5%, $P = 0.005$), although time to progression (4.1 and 3.1 months) and OS (12.5 and 13.3. months) were similar [14]. Forty percent of the capecitabine group showed grade 3 or 4 adverse reactions, including 18% with hand-foot syndrome. Oral fluoropyrimidine has been more convenient and can be administered in outpatient clinics to replace continuous infusion of 5-FU.

The addition of irinotecan, a specific inhibitor of topoisomerase I, or oxaliplatin, to the FU-LV combination resulted in improved OS, response rate, and time to progression compared to irinotecan alone, oxaliplatin alone, and 5-FU/LV alone [16–19]. FOLFIRI (5-FU/LV + irinotecan) and FOLFOX4 (5-FU/LV + oxaliplatin) as a first-line mCRC treatment had similar overall response rates (31% and 34%, respectively), time to progression (both 7 months), and OS (14 months and 15 months, respectively) [20]. FOLFIRI and FOLFOX have been widely prescribed to mCRC patients since 2004 [21]. With regard to bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), and cetuximab, a monoclonal antibody to epidermal growth factor receptor (EGFR), one study treated mCRC with bevacizumab plus FOLFIRI (OS, 20.3 months) and reported improved treatment efficacy compared to treatment without bevacizumab (OS, 15.6 months) [11]. Bevacizumab in combination with oxaliplatin improved PFS but not OS or response rate [22]. Cetuximab combined with FOLFIRI in patients with KRAS wild-type disease resulted in the significant improvement of OS, PFS, and response rate [23]. In 2004, bevacizumab and cetuximab were approved for mCRC, followed in 2006 by panitumumab, a human monoclonal IgG2 antibody to the EGFR. These biologic agents are administered combined with chemotherapy as current standard second- or third-line treatments. In two studies, the phase III FIRE-3 and the phase II PEAK, that compared the EGFR antibody and bevacizumab combined with chemotherapy in patients with KRAS exon 2 wild-type mCRC, median OS of the patients treated with chemotherapy plus cetuximab or panitumumab was longer than that of the patients with treated with chemotherapy plus bevacizumab. However, the PFS and response rates were not significantly different in these head-to-head trials [24,25]. In patients with RAS mutations (KRAS or NRAS), cetuximab and panitumumab cannot be used. Currently, there is no recommended standard sequence of chemotherapy and targeted biologics for mCRC patients. In the absence of evidence-based guidelines for sequencing therapy, the decision regarding first-line treatment has generally been based on patient factors and preferences, whereas subsequent treatments (after progression) are based on the treatment that was previously administered. Multiple lines of standard systemic therapy including combinations of chemotherapy and targeted therapy in patients with mCRC prolong OS time by approximately 30 months. However, many patients show good performance and need further anticancer therapy with minimal toxicity to control disease progression. In a CORRECT trial, the multikinase inhibitor regorafenib was suggested as a salvage therapy for patients who progressed after multiple lines of standard systemic therapy. Survival time of the regorafenib group was longer than that of the placebo group (6.4 months vs 5 months), but 17% of patients experienced grade 3 or 4 hand-foot syndrome and 37% reported diarrhea [26]. In 2015, TAS-102, a combination of a thymidine-based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor (tipiracil hydrochloride), was reported to have clinical efficacy for refractory CRC through a phase III trial; median OS was 7.1 months in the TAS-102 group and 5.3 months in the placebo group, and grade 3 or higher neutropenia occurred in 38% of the TAS group [27]. However, the patients who progress after second- and third-line standard chemotherapy show slow recovery of bone marrow and are fragile and weak. Thus, the side effects of salvage therapy should be minimized; the treatment should play the palliative role of relieving symptoms by reducing tumor burden and maintaining a good quality of life for the patients.

Preclinical studies of metronomic chemotherapy in CRC

In CRC cells and human CRC xenografts, the antiangiogenic and antitumor activities of metronomic irinotecan, oxaliplatin, and 5-fluorouracil and the metronomic combination of these drugs were investigated. Metronomic irinotecan alone inhibited tumor growth and decreased microvessel density but not 5-FU, oxaliplatin, and a combination of 3 drugs. The low-dose combination of 3 drugs showed a significant increase in VEGF secretion in CRC cells. These authors suggested that not all chemotherapeutic agents have antiangiogenic effects when administered metronomically [28]. In a preclinical study of metronomic irinotecan alone and combined with semaxanib, a VEGFR-2 tyrosine kinase inhibitor, the metronomic administration of SN-38, the active metabolite of irinotecan, inhibited tumor growth, decreased microvessel density, and increased thrombospondin-1(TSP-1) expression in colon cancer cells [29]. Irinotecan was administered intraperitoneally into mouse colon cancer xenografts in 3 regimens: (1) metronomic, 4 mg/kg^{-1} daily for 50 days; (2) at MTD, 100 mg/kg^{-1} 5 times weekly; or (3) an initial single dose of irinotecan 100 mg/kg^{-1} followed by metronomic 4 mg/kg^{-1} daily for 49 days. Tumor volume and microvessel density decreased the least with the initial dose of irinotecan 100 mg/kg followed by 4 mg/kg daily, and low-dose irinotecan inhibited tumor growth without toxicity.

In colon cancer mouse xenografts, circulating endothelial progenitor cells and microvessel density on day 15 were significantly inhibited with metronomic irinotecan (intraperitoneal injection of 10 mg/kg twice weekly) with and without bevacizumab (5 mg/kg twice weekly), but there was no significant difference on days 4 and 8 [30]. The authors of that study suggested circulating endothelial