Cancer Letters 400 (2017) 267–275

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Potential role of metronomic chemotherapy in the treatment of esophageal and gastroesophageal cancer

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ARTICLE INFO

Article history:
Received 26 October 2016
Received in revised form
9 January 2017
Accepted 11 January 2017

Keywords:
Metronomic
Esophagus
Gastric
Esophagogastric
Scheduling
Repurposing

ABSTRACT

Patients with esophagogastric cancer have poor prognoses in spite of the best available therapies. Patients are debilitated and may not tolerate, or may progress, on standard cytotoxic chemotherapy regimens. Metronomic chemotherapy is an attractive treatment option due to its very low reported toxicity, modest efficacy, low cost and ease of administration. Capecitabine is the most common drug used in metronomic scheduling; other drugs include cyclophosphamide and paclitaxel. Dosing of capecitabine can range from 1000 mg orally daily for 4 weeks on and 1 week off to a continuous dosing schedule of 1500 mg orally daily. Reported toxicities, including neutropenia, mucositis and hand-foot syndrome, occur in <10% of patients. As there is a lack of well-conducted, randomized clinical trials evaluating the role of metronomic chemotherapy in esophagogastric cancer, it cannot be recommended as the standard of care; however, it can be considered to be a therapeutic option, especially in elderly patients with relapsed disease for whom other therapeutic options are limited.

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Introduction

Although remarkable progress has been made in the systemic therapy of cancer, leading to a stepwise gradual prolongation of the expected overall survival (OS), we appear to have reached a therapeutic plateau in terms of efficacy of conventionally administered cytotoxic chemotherapy. Cancer researchers and clinicians have, therefore, resorted to exploring new therapeutic avenues including novel drugs, targeted agents, immunotherapy and drug repositioning, i.e., new ways to administer old medications. Metronomic therapy is one such means of drug repositioning. Conventionally, chemotherapeutic drugs are administered at or close to the maximal tolerated dose (MTD), which is determined through clinical trials. This dosing is repeated at a particular interval, commonly three weeks, to permit the patient to recover from the adverse effects of the chemotherapy. Thus, conventional chemotherapy entails the administration of intermittent high-dose pulses of chemotherapy with drug-free intervals in between. However, during the time that the patient recovers from the adverse effects of the conventionally dosed chemotherapy, the malignancy also has time to recover, and tumor regrowth and repopulation may occur, which potentially leads to drug resistance. Metronomic therapy refers to the administration of chemotherapeutic drugs at a lower dose than the MTD without prolonged drug-free intervals. Thus, metronomic administration allows exposure of the malignancy to a low dose of the chemotherapeutic drug on an almost continuous basis [1]. The mechanisms of action of metronomic chemotherapy have been postulated to be threefold: an antiangiogenic effect via action on the tumor endothelial cells, an induction of the tumor immune response and a promotion of tumor dormancy [2]. The use of metronomic chemotherapy has been described in almost all types of cancers, including head and neck cancer [3], lung cancer (both non-small cell [4] and small cell [5]), neuroendocrine tumors [6,7], esophageal cancer [8], breast cancer [9,10], brain tumors [11], liver cancer [12], colorectal cancer [13], prostate cancer [14], kidney cancer [15,16], ovary cancer [17,18], soft tissue sarcoma [19], pediatric solid tumors [20], lymphoma [21,22], leukemia [23,24] and melanoma [25]. Metronomic chemotherapy is an attractive option due to its very low reported toxicity, modest efficacy, low cost and ease of administration. These are very important considerations in most cancers; however, they assume a special significance in patients with esophagogastric cancer, which is known to have a very poor outcome and a high mortality rate. Esophageal cancer patients are usually debilitated (due to dysphagia caused by the primary

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http://dx.doi.org/10.1016/j.canlet.2017.01.017
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esophageal tumor leading to weight loss and malnutrition) and unable to tolerate toxic therapies. In this review article, we have attempted to summarize the data that are currently available on the use of metronomic chemotherapy in esophagogastric cancer, including the rationale, preclinical data, clinical experience and future directions.

Search strategy

A literature search of the Medline database was performed using the search terms "metronomic chemotherapy", "esophagogastric", "esophageal", "esophagus", "gastric" and "gastrointestinal". English language publications were selected. The references of the selected papers were manually searched for additional relevant studies. We searched the ClinicalTrials.gov database and the Clinical Trials Registry-India (CTRI.nic.in) database using the search word "metronomic" to identify any ongoing trials. We checked all the studies that were displayed and selected the studies that were relevant to patients with esophageal and gastroesophageal cancer. The search was performed up to Nov 2016.

Unmet need

In spite of the best available therapies, patients with esophagogastric cancer do poorly. Expected overall survival (OS) for patients with early stage disease who are treated with radical surgery ranges from 11 to 24 months. Patients treated with radical concurrent chemoradiotherapy have an expected OS of 14 months, and patients with unresectable advanced or metastatic disease have an expected median OS of 6–7 months [26,27]. Thus, there is a tremendous scope for improvement in therapeutics for esophagogastric cancer at every stage of the disease.

There are several reasons for the poor prognosis of esophagogastric cancer patients. Esophagogastric cancer is a systemic disease even at an early stage. Bobek et al. reported the presence of circulating tumor cells in almost 70% of patients with resectable esophageal cancer [28]. The landmark ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) showed a near doubling of survival when induction chemoradiotherapy was added to surgery in patients with localized disease thus underscoring the need to add therapy, in the form of both locoregional (radiotherapy) and systemic therapy (chemotherapy), to radical surgery [29]. The stumbling block stems from the fact that most patients are debilitated following radical aggressive therapies, such as surgery and chemoradiotherapy, rendering the administration of full-dose cytotoxic chemotherapy nearly impossible. In the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, the addition of perioperative epirubicin, cisplatin and 5-fluorouracil (5FU) chemotherapy in patients with resectable gastroesophageal cancer had a demonstrated survival advantage; however, of the 250 patients assigned to perioperative chemotherapy, only 137 patients (54.8%) began postoperative chemotherapy, and 104 patients (41.6%) eventually completed the planned postoperative chemotherapy. Thus, less than half of the patients were able to complete systemic cytotoxic therapy in the postoperative setting [30]. Following radical chemoradiotherapy, the local failure rate is approximately 45% with a median OS of 14.1 months. Researchers have attempted various approaches to improve the outcome of these patients who receive chemoradiotherapy, including increasing the dose of radiation, altering the radiotherapy fractionation, adding brachytherapy, intensifying chemotherapy and adding neoadjuvant chemotherapy [27]. Unfortunately, none of these methods has convincingly improved outcomes. In the palliative setting, patients have very poor expected survival. Additionally, most patients are debilitated, have poor general condition and are unable to tolerate combination cytotoxic chemotherapy regimens. Thus, at every stage of esophagogastric cancer, there exists a window of opportunity in which an appropriate intervention may improve outcomes. Metronomic chemotherapy may be considered as one of the possible interventions in these patients.

Mechanism of action of metronomic chemotherapy and rationale for use in esophagogastric cancer

Tumor angiogenesis and neovascularization are important emerging concepts. Vascular endothelial growth factor (VEGF) overexpression has been demonstrated in many solid tumors, including esophagogastric cancer, and may lead to a poor prognosis [31]. Targeting the VEGF pathway with conventional antiangiogenic agents, such as bevacizumab, has not significantly prolonged OS in patients with advanced esophagogastric cancer [32]. Ramucirumab, a humanized monoclonal antibody to the extracellular domain of VEGFR-2, has been studied in the relapsed setting in patients with gastric cancer both as monotherapy (REGARD study) and in combination with paclitaxel chemotherapy (RAINBOW study) [33,34]. Both studies showed a small prolongation in OS as a result of ramucirumab with the magnitude of benefit ranging from 1.4 to 2.2 months. However, this small improvement in efficacy came at a significant cost and with possible toxicities of hypertension, gastrointestinal perforation, neutropenia and nephropathy. An alternative means to target the VEGF pathway and angiogenesis would be through metronomic chemotherapy. Low doses of chemotherapeutic agents have been shown to selectively inhibit activated endothelial cells. Additionally, metronomically administered low-dose chemotherapeutic drugs upregulate endogenous angiogenesis inhibitors, such as thrombospondin 1 [35]. Yuan et al. studied the effect of metronomically administered capecitabine in gastric cancer cell lines. These researchers observed that metronomically administered 5FU did not lead to significant cytotoxicity, i.e., tumor apoptosis and cell death; rather, it significantly lowered the levels of secretory angiogenesis factors and inhibited the growth of vascular endothelial cell small tube formation. In contrast, conventional chemotherapy caused an increased VEGF level probably reflecting a rebound increase in angiogenesis during the treatment-free interval between cycles [36].

Targeting the immune system is another proposed mechanism of action of metronomic chemotherapy. The interplay of tumors and the immune system is complex and is reflected in the heterogeneous nature of immune infiltrates that occur in various tumor types [37–39]. Several studies have revealed that the presence of effector T-cells, specifically T_H17 cells, predicts for a good prognosis in patients with esophageal and gastric cancers [40]. Enomoto et al. found that the presence of tumor-infiltrating memory T-cells in esophageal squamous cell carcinoma CD45RO+ positively correlated with disease-free survival and OS [41]. Conventional cytotoxic chemotherapy leads to destruction of the tumor cells; however, it also leads to death of immune cells resulting in immunosuppression. This immune system destruction has the paradoxical effect of promoting tumor growth in between chemotherapy cycles and after chemotherapy. When chemotherapy causes death of the tumor cells, dendritic cells take up the tumor antigens and present them to T-cells, which are subsequently primed to be cytotoxic to the tumor cells. Thus, a delicate balance needs to be struck between tumor cell cytotoxicity and promotion of antitumor immunity at low doses of chemotherapy, while cytotoxicity to both the tumor cells and the immune cells must be balanced at higher doses of chemotherapy. Metronomic chemotherapy is administered in low doses and does not abrogate antitumor immunity. Certain chemotherapeutic drugs, such as

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