RESEARCH ARTICLE

Pemetrexed is Mildly Active with Good Tolerability for Treatment of Patients with Colorectal Cancer

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Abstract

Purpose: This systematic analysis was conducted to evaluate the efficacy and safety of pemetrexed based salvage chemotherapy for treatment of patients with metastatic colorectal cancer. Methods: Clinical studies evaluating the efficacy and safety of pemetrexed based regimens on response and safety for patients with colorectal cancer were identified using a predefined search strategy. Pooled response rates (RRs) were calculated. Results: For pemetrexed based regimens, 4 clinical studies including 201 patients with advanced colorectal cancer were considered eligible for inclusion. The analysis suggested that, in all patients, pooled RR was 20.4% (41/201). Major adverse effects were neutropenia, anorexia, fatigue, and anemia. No treatment related death occurred with pemetrexed based treatment. Conclusion: This systematic analysis suggests that pemetrexed based regimens are associated with mild activity with good tolerability in treating patients with metastatic colorectal cancer.

Keywords: Metastatic colorectal cancer - pemetrexed chemotherapy - response rate

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Introduction

Colorectal cancer (CRC) is considered to be a main cause of malignancy-related death in the world (Parkin et al., 2001). and in China (Sung et al., 2005). Patients with early staged disease could be surgical resected, however, those with advanced disease have to be treated by chemotherapy. At present, Guideline based chemotherapeutic treatment (NCCN, 2012). for the management of patients with advanced colorectal cancer are chemotherapeutic regimens containing: fluorouracil 5-FU, oxalipatin, irinotecan, oxalipatin, and cetuximab, etc. And reported strategies for patients in this setting is to combine these agents to establish regimens , eg, FOLFIRI, FOLFOX, XELOX, xeloda and irinotecan, S-1 and irinotecan, UFT/LV and irinotecan/oxalipatin, etc (Xu et al., 2011). However, which chemotherapy regimen can be more effective is not clear.

Pemetrexed is a novel, multi-targeted antifolate that inhibits several folate-dependent enzymes involved in the de novo pathways of pyrimidine and purine biosynthesis (Shih et al., 1997). Its primary mechanism of action is the inhibition of thymidylate synthase, which results in decreased thymidine being necessary for DNA synthesis (Schilsky et al., 1992; Shih et al., 1992). Pemetrexed is also a potent inhibitor of dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, enzymes involved in purine synthesis. Pemetrexed has demonstrated broad antitumor activity in a variety of in vitro tumor cell lines, and is active against lymphoma, colon, lung, pancreas and breast cancer xenografts in vivo (Shih et al., 1999; Hanauske et al., 2001). On the basis of previous clinical phase I studies, a schedule of 600 mg/m^2 pemetrexed given as a 10-min infusion once every 21 days was the recommended regimen for further development o single-agent pemetrexed (Renaldo et al., 1995; Ronald et al., 1999). Phase II studies have yielded response rates ranging from 6% to 31% in a wide variety of tumors (Adjani et al., 2003). According to this background, we hypothesize that pemetrexed originated regimen could be established as an optimal schedule for patients with advanced colorectal cancer. The primary goal of evidence based study was to investigate the potential benefit and safety associated with pemetrexed combined chemotherapy in treating patients with advanced colorectal cancer.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (colorectal cancer) and (pemetrexed). All clinical studies evaluating the impact of pemetrexed on the response or survival and side effects for colorectal

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cancer published in English prior to July 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (a) clinical studies, conbined with irinotecan, or a platinum; (b) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced colorectal cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 114 papers relevant to the search words by the end of April, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (John et al., 2000; Atkins et al., 2005; Underhill et al., 2007; Louvet et al., 2010) when pemetrexed was in chemotherapy. These studies had been carried out in China, Europe countries, and the United States. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of pemetrexed as first line chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Atkins JN et al. was 29.6%, of John et al. was 15.4% and 13.6%, of Louvet et al. was 20%, of Underhill et al. Totally, 201 patients were enrolled and 41 patients achieved CR or PR, the pooled response rate thus was 41/201 (20.4%). Observation on toxicities: major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity.

Discussion

Colorectal cancer remains a significant problem for global health as it is one of the most common cause of tumor-related death world-wide (Fouz et al., 2013; Engin et al., 2013; Sedighi et al., 2013; Zhu et al., 2013; Wu et al , 2014; Cabuk et al., 2014; Chin et al., 2014; Fouladi et al., 2014; Majeed et al., 2014; Gogia et al., 2014; Liu et al., 2014; Louisa et al., 2014; Moazzezy et al., 2014; Niu et al., 2014; Rizalar et al., 2014; Sipetic-Grujicic et al., 2014; Prajoko et al., 2014; Inanc et al., 2014; Varol et al., 2014; Yadav et al., 2014). The standard treatment for metastatic colorectal cancer is 5-FU or 5-FU combinations. Response rates to 5-FU alone are less than 20%, while combination regimens with biochemical modulating agents (i.e., leucovorin) improved response rate. Now, multiple other agents are available for the treatment of metastatic colorectal cancer. These agents include UFT, capecitabine, CPT-11, oxaliplatin and raltitrexed. It is considered that these chemotherapeutic agents have predictable toxicities and similar response rates. Based on phase II data, UFT gave a response rate around 30% with a median time to progression of 7.4 months and a median survival time of 14.2 months (Abad et al., 1997). Oxaliplatin, a commonly used drug for colorectal cancer, has a response rate of 57% and a progression-free survival of 39.6 weeks when combined with 5-FU and leucovorin (De Gramont et al., 1998). Despite the limited availability of preclinical data, the association of pemetrexed (500 mg/m^2) and oxaliplatin (120 mg/m^2), every 21 days for 6 cycles, was studied as first-line therapy in a phase II trial, reporting a clinical response rate of 29.6% in patients with metastatic adenocarcinoma of the colon or rectum (Atkins et al., 2005).

Irinotecan is an agent available for treatment in metastatic colorectal cancer (Conti et al., 1996). Prospective, randomized trials in colorectal cancer suggested that irinotecan gave a response rate of 22% and a statistically improved difference in response when compared to best supportive care in patients who had failed 5-FU based chemotherapy (Cunningham et al., 1998).

Pemetrexed is a multitargeted antifolate agent that inhibits several key folate-dependent enzymes required for de novo purine and/or pyrimidine biosynthesis, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih et al., 1997). Pemetrexed has shown broad clinical antitumor activity in patients with colorectal, pancreatic, and breast cancers (Adjei et al., 2004) and has received regulatory approvals for treating patients with malignant mesothelioma and nonsmall cell lung cancer (Hazarika et al., 2004). Pemetrexed 500-600mg/m^2 administered every three weeks showed single-agent activity as first-line treatment for advanced CRC in two phase II trials (Cripps et al., 1999; John et al., 2000). The objective responses rates were 15% in the American study (John et al., 2000) and 17% in the Canadian study (Cripps et al., 1999) and the median overall survival times were 16.2 and 15.1 months, respectively. The major toxicities of pemetrexed are myelosuppression, skin rash, and mucositis, with neutropenia being the primary dose-limiting toxicity (Louvet et al., 2004). An elevated level of plasma homocysteine was found to be a significant risk factor for treatment-related toxicities (Niyikiza et al., 2002). Supplementation with vitamin and folic acid has been shown to lower plasma homocysteine level and improve the toxicity of pemetrexed.

The distinct mechanisms of action and patterns of resistance displayed by pemetrexed and irinotecan make them attractive agents for combination therapy in mCRC patients. The combination of pemetrexed and irinotecan, administered every three weeks, was shown to be feasible in phase I studies (Hochster et al., 2005; Rowinsky et al., 2007). In the phase I/II study reported by Hochster et al., pemetrexed 500mg/m^2 followed by irinotecan 300mg/m^2 on day 1, every 21 days, induced an objective response rate of 11% in 35 patients previously treated with 5-FU-based chemotherapy for advanced disease (Hochster et al., 2005).

Our systemic analysis suggested that pemetrexed based regimens, 4 clinical studies which including 201 patients with advanced colorectal cancer were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 20.4% (41/201) in pemetrexed based regimens. Major adverse effects were neutropenia, anorexia, fatigue, and anemia in pemetrexed based treatment. No treatment related death occurred in pemetrexed based treatment. In conclusion, this systemic analysis suggests that pemetrexed based regimens are associated with mild active with good tolerability in treating patients with metastatic colorectal cancer.

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