RESEARCH ARTICLE

Pemetrexed is Mildly Active with Good Tolerability in Treating Patients with Gastric Cancer

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Abstract

Background: This systemic analysis was conducted to evaluate the efficacy and safety of pemetrexed based chemotherapy in treating patients with metastatic gastric cancer (MGC) as a salvage chemotherapy. Methods: Clinical studies evaluating the efficacy and safety of pemetrexed based regimens on response and safety for patients with gastric cancer were identified by using a predefined search strategy. Pooled response rates (RRs) of treatment were calculated. Results: In pemetrexed based regimens, 4 clinical studies including 171 patients with advanced gastric cancer were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 25.1% (43/171) in pemetrexed based regimens. Major adverse effects were neutropenia, anorexia, fatigue, and anemia. No treatment related death occurred in pemetrexed based treatment. Conclusion: This systemic analysis suggests that pemetrexed based regimens are associated with mild activity with good tolerability in treating patients with MGC.

Keywords: Pemetrexed - gastric cancer

Asian Pac J Cancer Prev, **15 (17)**, 7137-7139

Introduction

According to an estimate on cancer incidences and mortalities in China in 2010, the National Central Cancer Registry of China evaluated data for the year of 2010 from 145 qualified cancer registries covering 158,403, 248 people. The estimates of new cancer cases and cancer deaths were 3,093,039 and 1,956,622, respectively (Chen et al., 2014). The incidence and mortality rate of gastric cancer are still high over the last several decades (Yu et al., 2007). Despite advances in prevention, risk factor reduction, early diagnosis and treatment, gastric cancer remains a main public health concern. It was estimated that 121, 269 new cases of gastric cancer were diagnosed in China in 2000 and 168, 013 in 2005 (Ferlay et al., 2002; Huang et al., 2004; Yang et al., 2005).

Now, combined chemotherapy is mostly prescribed in adjuvant and in metastatic settings of gastric cancer. Although 5-Fu represented the gold standard from 1970s, oxaliplatin-based regimens are the mainstay of adjuvant and paliative chemotherapy for gastric cancer since 2000s. When single-agent chemotherapy was used in conventiona resistant metastatic setting, agents considered to be active include irinotecan, paclitaxel, cisplatin and pemetrexed. Response rates are ranged from 0-38% (Akram et al., 2012).

Pemetrexed is a recently developed antifolate agent with a favorable toxicity profile, and could be well tolerated in patients who were treated with third- or further-line treatment (Pozzo et al., 2008). Although activity of pemetrexed against breast, gastric, pancreatic and colorectal adenocarcinoma cell lines was reported (Adjei, 2004), only several phase I or II studies containing pemetrexed were conducted for patients with gastric cancer, with a response rate ranging from 13.04% to 36.36% (Bajetta et al., 2003; Kim et al., 2008; Celio et al., 2009; Chen et al., 2010; Wei et al., 2013). In a previous study conducted in China (Wei et al., 2013), patients who were staged IV and failed treatment with fluorouracil based chemotherapy, and then received pemetrexed based combination therapy as second, third, or 4th lines. Overall, Three patients (13%, two as second line and one as third line) achieved PR, while five patients (22%) remained stable, progression of disease, with no completer emission, RR was 13%, DCR 35%. Toxicity of pemetrexed based combination therapy was mild. Main toxicity was myelosuppressionin in this trial. Three to 4 grade neutropenia, anemia and thrombocytopenia were 13%, 8.7% and 4.3% respectively.

According to this background, we hypothesize that pemetrexed originated regimen could be established as an optimal schedule for patients with metastatic gastric cancer (MGC).

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (gastric cancer) and (pemetrexed). All clinical studies evaluating the impact of pemetrexed on

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the response or survival and side effects for advanced gastric 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: (1) clinical studies, conbined with gemcitabine, epirubicine or a platinum; (2) 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 gastric 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: (1) duplicate data; (2) 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 4 papers relevant to the search words by the end of July, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Bajetta et al., 2003; Celio et al., 2009; Chen et al., 2010; Wei et al., 2013) when pemetrexed was in chemotherapy. These studies had been carried out in China, Taiwan, Italy. 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 chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Wei et al. (2013) was 13.04%, of Chen et al. (2013) was 23.53%, of Bajetta et al. (2003) was 22.22%, of Celio et al. (2009) was 36.36%. Totally, 171 patients were enrolled and 43patients achieved CR or PR, the pooled response rate thus was 43/171 (25.15%).

Observation on toxicities: major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity.

Discussion

Gastric cancer is a common disease in Asian Pacific area, and most medical resources are specially focused on the diagnosis and treatment of this disease (Ahmad et al., 2013; Atrkar-Roushan et al., 2013; Ma et al., 2013; Song et al., 2013; Suh et al., 2013; Tuncel et al., 2013; Yang et al., 2013; Yang et al., 2013; Zare et al., 2013; Zhang et al., 2013; Zhu et al., 2013). Combined chemotherapy was reported to be superior to the best supportive care in the man¬agement of MGC (Pyrhonen et al., 1995; Jo et al., 2007; Chen et al., 2013; Usakova et al., 2013). The various combination chemotherapy regimens as first-line treatment showed response rates of 35-45%, and a median pro¬gression-free survival of 5-6 months. And the regimen of cisplatin and fluorouracil combi¬nation was regarded as a standard chemo¬therapy in the fist line treatment. Studies of second line chemotherapy reported an overall survival ranging from 5 to 9 months and a progression free survival ranging from 2 to 4 months (Nguyen et al., 2006; Jo et al., 2007; Park et al., 2008; Seo et al., 2008; Fiala et al., 2013). There is no standard second line treatment for these patients.

Although some agents, e.g. taxanes and CPT-11 have shown encouraging anti-tumor activity in MGC patients, these regimens are inevitably accom¬panied by substantial toxicities, which reduce the value as a palliative treatment, especially in second line treatment for patients with relative poor clinical condition. Therefore, the need for new regimens with improved efficacy and safety is increasing for patients who have failed first line treatment. Pemetrexed is a novel multitargeted antifolate that inhibits several enzymes in the de novo pathways of pyrimidine and purine biosynthesis, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide ormyltransferase. Pemetrexed demonstrated activity in a variety of tumor types based on previous reports, including non-small cell lung cancer, malignant pleural mesothelioma, pancreas, colorectal, gastric, bladder, breast, and head and neck cancers (Martin, 2006).

Pemetrexed has been tested by previous phase II trials in MGC patients and shown an activity of around 20% with minimal or no prior chemotherapy: the response rate of Wei et al. (2013) was 13.04%, of Chen et al. (2013) was 23.53%, of Bajetta et al. (2003) was 22.22%, of Celio et al. (2009) was 36.36%. Thus, a correlation could exist between thymidylate synthase tumor expression with pemetrexed antitumor activityis; and this hypothesis is supported by this current study.

The main toxicities of pemetrexed are myelosuppression, skin rash, and mucositis. Addition of folic acid and vitamin B12 significantly reduced the toxicity of pemetrexed, especially hematologic toxicity and gastrointestinal toxicity. Pemetrexed is the expected agent for use in high risk patients, especially elderly or poor performance status patients (Wei et al., 2013). Hematological toxicity was considerable, and thrombocytopenia was the most prominent toxicity. The majority of patients experienced grade 4 thrombocytopenia (Wei et al., 2013). The count of leukocyte and platelet returned to normal after the treatment of colony-stimulating factor, interleukin 11 and recombinant human thrombopoietin.

From previous study, digestive tract reaction ranged from 1 to 2 could be alleviated by symptomatic treatment.

By hepatoprotective medications, transaminase could return to normal. For patients had oral mucositis, with the supplements of vitamins and oral care, the oral mucosal healing with no fungal infection. For patient had rash with pruritus, rash subsided gradually after symptomatic treatment of the antipruritic and anti allergic.

In conclusion, this systemic analysis suggests that pemetrexed based regimens are associated with mild active with good tolerability in treating patients with metastatic gastric cancer. Future studies with a randomized controlled group are needed to further evaluate the efficacy and tolerability of pemetrexed in this setting.

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