RESEARCH ARTICLE

# Systematic Analysis of Pemetrexed-based Chemoradiotherapy for Patients with Locally Advanced or Metastatic Esophageal Cancer

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## Abstract

**Purpose: This systematic analysis was conducted to evaluate the efficacy and safety of pemetrexed-based chemoradiotherapy in treating patients with locally advanced or metastatic esophageal cancer. Methods: Clinical studies evaluating the efficacy and safety of pemetrexed based regimens on response and safety for relevant patients were identified using a predefined search strategy. Pooled response rates (RRs) were calculated. Results: For pemetrexed-based regimens, 4 clinical studies including 47 patients with locally advanced or metastatic esophageal cancer were considered eligible for inclusion. Systematic analysis showed that, in all patients, the pooled RR was 51% (24/47) . Major adverse effects of grade III/IV were esophagitis, neutropenia, thrombocytopenia, anemia anorexia, fatigue, diarrhea, dysphagia and vomiting. No treatment related death occurred with pemetrexed-based treatment. Conclusion: This systematic analysis suggests that pemetrexed based radiotherapy is associated with reasonable activity and good tolerability in treating patients with locally advanced or metastatic esophageal cancer.**

**Keywords:** Metastatic esophageal cancer - pemetrexed-based chemoradiotherapy - efficacy - tolerability

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## Introduction

The incidence of esophageal cancer is ranked eighth world widely, sixth in mortality (Tang et al., 2014). According to Chinese National Cancer Registry, the incidence of esophageal cancer (EC) is sixth and mortality fourth, with incidence and mortality rates significantly on the rise (Tang et al., 2014).

However, standard chemotherapy for EC has not yet been established, because of the absence of enough clinical evidence from randomized phase III trail. It is reported that combined chemotherapy could obtain a response rate of 20%-80% with chemotherapeutic agent eg., paclitaxel, cisplatin and/or 5-Fu, etc. (Polee et al., 2002; Bucci et al., 2004 ; Orditura et al., 2010; Mirinezhad et al., 2012). Low-dose, continuous infusional paclitaxel is reported to maximally inhibit cancer through reducing the emergence of drug-resistant tumor cells (Shade et al., 1998-1999). After an initial report with a response rate of 27% among taxane-resistant patients with breast cancer (Seidman et al., 1996), subsequent trials suggested that the treatment efficacy was improved (Holmes et al., 1998). First-line paclitaxel administered as a prolonged infusion (35 mg/m2/24 h continuously infused over 96 h ) in advanced bronchioloalveolar carcinoma (BAC) is active (SWOG 9714). The objective response rate was 14% (all partial responses); 40% of patients demonstrated stable disease. The median progression-free and overall survivals were 5 and 12 months, respectively (West et al., 2005). Twenty four hour continuous infusional paclitaxel combination with oxaliplatin in treating 30 Chinese patients with III-IV stage advanced esophageal squamous cell cancer achieved 4 CR, 14 PR, and 4 SD, with RR 60. 0% (Wang et al., 2010). But the side effects were focused of consideration.

Pemetrexed is a recently developed antifolate agent with a favorable toxicity profile, and could be well tolerated for patients who were treated with third- or further-line treatment (Pozzo et al., 2008). Although activity of pemetrexed against breast, gastric, esophageal, pancreatic and colorectal adenocarcinoma cell lines was reported (Adjei, 2004), only several phase I or II studies containing pemetrexed were conducted for patients with locally advanced or metastatic esophageal cancer, with a response rate ranging from 23% to 90% (Li et al., 2011; Jatoi et al., 2010; Katipamula et al., 2008; Seiwert et al., 2007). In a previous study conducted in China (Li et al., 2011), 12 patients with T3-4N0-1M0-1a thoracic esophageal EC were included. The total dose of selective lymph node with late course accelerated hyperfractionated by intensity modulated radiotherapy was 59.6 Gy/34 fractions in 5.4 weeks. The concurrent chemotherapy protocol was as following: cisplatin 10 mg/m$^2$ on days 1-5 and 22-26, pemetrexed in escalating doses, from the base level of 500 mg/m$^2$ once every 21 days (Li et al., 2011).

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As a result, three patients were enrolled in dose level with pemetrexed 500 mg/m$^2$ and nine patients in dose level with 400 mg/m$^2$, respectively. In this study, complete response and partial response were observed in eight and four patients, respectively. Furthermore, no patient experienced cancer progression with a median follow-up of 9 months. In this study, the concurrent selective lymph node with late course accelerated hyperfractionated by intensity modulated radio and chemotherapy is feasible, although toxicities were common, it is still suggested that pemetrexed based chemo radiotherapy was safe, well tolerated, and could achieve an encouraging outcome (Li et al., 2011).

According to this background, we hypothesize that pemetrexed originated chemo radiotherapy could be established as an optimal schedule for treating patients with locally advanced or metastatic esophageal cancer.

## Materials and Methods

*Search strategy*

We searched PUBMED, by using the following search term: (esophageal cancer) and (pemetrexed). All clinical studies evaluating the impact of pemetrexed on esophageal 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 paclitaxel 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 esophageal 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 August, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Seiwert et al., 2007; Katipamula et al., 2008; Jatoi et al., 2010; Li et al., 2011) when pemetrexed was used in chemo radiotherapy. These studies had been carried out in China, and the USA. 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 chemo radiotherapy, studies included in this study are presented as short-term outcomes: the response rate of Li et al. (2011) was 100%, of Jatoi et al. (2010) was 23.0%, of Katipamula et al. (2008) was 67%, of Seiwert et al. (2007) was 67%. Totally, 47 patients were enrolled and 24 patients achieved CR or PR, the pooled response rate thus was 24/47 (51%).

Observation on toxicities of grade III/IV were esophagitis, neutropenia, thrombocytopenia, anemia anorexia, fatigue, diarrhea, hepatorenal dysfunction, dysphagia and vomiting. No treatment related death occurred in pemetrexed based treatment.

## Discussion

At present, EC ranks the 8th according to the incidence of malignant tumors all over the world and patients with esophageal cancer in China accounts for more than 50%, with the cancer related mortality ranking the 4th, highly occurring in Hennan Province of China (Malik et al., 2014; Somi et al., 2014; Yang et al., 2014; Yuan et al., 2014; Zheng et al., 2014). About 50% of patients with EC were found with advanced disease at diagnosis, with unfavorable prognosis, and 5%~7% five-year survival rate (Jiang et al., 2014; Wang et al., 2014). Additionally, even though patients accepted surgical treatment, there still exists postoperative recurrence and metastasis in nearly 90% of patients. Fifty percent of patients in early stage recurs within 5 years and the autopsy confirmed that there appeared distant metastasis in 50% patients with local advanced esophageal cancer (Liu et al., 2009). Therefore, chemotherapy plays an important role in the treatment of esophageal cancer, with the intention to control the metastasis of tumor. In last decade, large-scale randomized controlled trials on esophageal cancer have proved that chemotherapy could improve long-term 5-year survival rate of esophageal cancer.

However, the survival and local control rates of EC are disappointing if only single modality are considered , thus led to a need to develop more effective nonsurgical management that is definitive chemoradiotherapy (Tsuya et al., 1968). It is suggested that chemoradiotherapy was significantly superior to radiotherapy alone (Wong et al., 2003). Concurrent chemoradiotherapy reduced the mortality of 9% and 8% in patients with stageIa and IIa respectively, and improved local control rate (Wong et al., 2003).

Chemotherapeutants incorporated into chemoradiotherapy include 5-fluorouracil (5-FU), cisplatin, and mitomycin C (MMC), and taxane-based regimens were investigated as a less toxic alternative to 5-FU-based regimens. The taxanes had been identified as potential radiosensitizers when preclinical data revealed

their lethal effects of inhibiting mitosis, interfering with the cell cycle, and encouraging apoptosis (Herscher et al., 1999). Taxane was shown to have significant activity in patients with metastatic esophageal cancer in the early 1990s (Ajani et al., 1994). Multiple phase II studies have evaluated taxane-based chemoradiotherapy regimens in esophageal cancer. These studies and other retrospective analyses support the conclusion that taxane-based regimens result in complete response rates and survival comparable to those attained using 5-FU-based regimens (Kelsey et al., 2007). In addition, data show that rates of grade 4 esophagitis in these regimens are 5% or less (Safran et al., 2007). Conventional radiotherapy does not concentrate adequate dose on the tumor, thus is associated with increased toxicities, especially when combined with chemotherapy. On the other hand, three-dimensional conformal external beam radiotherapy makes the dose distribution of target more reasonably and reduces radiation associated toxicities.

In terms of Chemotherapy, pemetrexed has been tested by previous phase II trials in EC patients and shown an activity from 20% to more than 80% with minimal or no prior chemotherapy: the response rate of Li et al. (2011) was 100%, of Jatoi et al. (2010) was 23.0%, of Katipamula et al. (2008) was 67%, of Seiwert et al. (2007) was 67%.. The current systemic analysis suggested that, in all patients, pooled RR was 51% (24/47) in pemetrexed based regimens. Toxicities were general mild; with reported grade III/IV were esophagitis, neutropenia, thrombocytopenia, anemia anorexia, fatigue, diarrhea, dysphagia and vomiting. No treatment related death occurred in pemetrexed based treatment.

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 radiotherapy are associated with reasonable activity with good tolerability in treating patients with locally advanced or metastatic esophageal 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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