RESEARCH ARTICLE

Pemetrexed in Treating Patients with Metastatic Bladder Cancer

Qing Li[&], Jian-Zhang Li[&], Wan-Hai Xu, Lin Gao*

Abstract

Background: This pooled analysis was conducted to evaluate the efficacy and safety of pemetrexed based chemotherapy in treating patients with metastatic bladder cancer as salvage chemotherapy. Methods: Clinical studies evaluating the efficacy and safety of pemetrexed based regimens on response and safety for patients with bladder cancer were identified by using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. Results: In pemetrexed based regimens, 3 clinical studies which including 105 patients with advanced transitional cell cancer of the urothelium were considered eligible for inclusion. Pooled analysis suggested that, in all patients, pooled RR was 26.7% (28/105) for pemetrexed based regimens. Major adverse effects were neutropenia, anorexia, fatigue, and anemia in pemetrexed based treatment. Two treatment related deaths occurred with pemetrexed based treatment. Conclusion: This pooled analysis suggests that pemetrexed based regimens are associated with mild activity and good tolerability in treating patients with metastatic bladder cancer.

Keywords: Pemetrexed - metastatic bladder cancer

Asian Pac J Cancer Prev, **16 (9)**, 3839-3841

Introduction

Urothelial cancer ranks the fourth most common cancer and could occur along urinary tract (Munoz et al., 2000; Ploeg et al., 2009). Within these, bladder cancer accounts for 95% of urothelial cancer (Munoz et al., 2000; Ploeg et al., 2009). It is reported that 15-20% of bladder tumors are invasive (Babjuk et al., 2011; Margulis et al., 2009). Over the last 15 years, a number of new agents and combination regimens have been tested in advanced urothelial cancer. For example, paclitaxel, pemetrexed and docetaxel are exhibiting activity against advanced transitional cell carcinoma, although none of the doublets/triple combinations studied to date have demonstrated improved survival compared to the M-VAC regimen (Roth et al., 1994; Sweeney et al., 2006; McCaffrey et al., 1997; Bamias et al., 2004). Another therapeutic dilemma is that patients with advanced urothelial caner may have impairment in renal function due to age, comorbid conditions and/or disease related factors which limit the utility of cisplatin-based regimens.

Pemetrexed is a recently developed antifolate agent with a favorable toxicity profile, and could be well tolerated for patients with multiple sites of cancer who were treated with third- or further-line chemotherapy (Tian et al., 2014; Liu et al., 2014; Wu et al., 2014; Huang et al., 2014; Lu et al., 2013; Wei et al., 2013). 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 bladder cancer, with a response rate ranging from 8% to 31.8% (Dreicer et al., 2008; Galsky et al., 2007; Sweeney et al., 2006).

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 baldder cancer.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (metastatic bladder cancer) and (pemetrexed). All clinical studies evaluating the impact of pemetrexed on metastatic bladder cancer. Published in English prior to December 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

*Department of Urology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China [&]Equal contributors *For correspondence: chunzhisheng077@sina.com*

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 bladder 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 3 papers relevant to the search words by the end of December, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Dreicer et al., 2008; Galsky et al., 2007; Sweeney et al., 2006) when pemetrexed was used in chemotherapy. These studies had been carried out in 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 chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Dreicer et al. (2008) was 31.8%, of Galsky et al. (2007) was 8.0%, and of Sweeney et al. (2006) was 27.7%. Totally, 105 patients were enrolled and 24 patients achieved CR or PR, the pooled response rate thus was 26.7% (28/105).

Observation on toxicities included febrile neutropenia, thrombocytopenia, anemia anorexia, fatigue, diarrhea, dysphagia and vomiting. Two treatment related death occurred in pemetrexed based treatment.

Discussion

Initial chemotherapy for patients with metastatic transitional cell carcinoma includes M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) and is gradually been replaced by gemcitabine + cisplatin (GC) according to a phase III trial comparing M-VAC to GC which demonstrated comparable activity with a somewhat improved toxicity profile favoring GC (von der Maase et al., 2000). 1a

Pemetrexed has been tested by previous phase II trials for patients with metastatic bladder cancer. In a previous study published in 2008, Dreicer et al. conducted a phase 2 study to assess the efficacy and safety of pemetrexed and gemcitabine in patients with advanced urothelial cancer who were previously untreated for metastatic disease (Dreicer et al., 2008). They treated 113 46 patients with advanced urothelial carcinoma who received 500 mg/m2 pemetrexed intravenously on day 1, and 1000 mg/m2 gemcitabine intravenously on day 1 and day 8 (Dreicer et al., 2008). Their results suggested that 2 patients attained a complete response, and 12 patients attained a partial response for an overall response rate of 31.8%. The median time to disease progression was 5.8 months, and the median overall survival was 13.4 months. The main toxicity was neutropenia, including febrile neutropenia. And 2 therapy-related deaths were reported (Dreicer et al., 2008). Thus, they concluded that the combination of pemetrexed and gemcitabine was moderate active in this cohort of patients at the expense of significant myelosuppression.

In another study, Galsky et al. treated 13 patients with advanced urothelial carcinoma, to determine the activity of pemetrexed used as second-line therapy in patients with advanced urothelial carcinoma that had relapsed after receiving perioperative chemotherapy, or progressed on first-line chemotherapy for metastatic disease (Galsky et al., 2007). Patients received pemetrexed 500 mg/m2 every 21 days along with folic acid and vitamin B12 supplementation (Galsky et al., 2007). In their results, A total of 13 patients were enrolled. An objective response was achieved in 1/12 evaluable patients for an overall response rate of 8% (90% upper limit 29%). This level of activity did not meet criteria for expansion based on the pre-defined optimal 2-stage Simon design and the trial was concluded. Treatment was generally well tolerated, however, 2/13 patients developed febrile neutropenia. Non-hematologic grade > or = 3 toxicity was rare (Galsky et al., 2007). Therefore, they concluded that pemetrexed as second-line therapy in advanced urothelial carcinoma is associated with modest activity, and suggested that further investigation should be conducted to analyze the role of pemetrexed in these patients (Galsky et al., 2007).

With a purpose to assess the antitumor activity and toxicity of pemetrexed as second-line chemotherapy in patients with locally advanced or metastatic transitional cell carcinoma of the urothelium, Sweeney et al conducted a phase II study (Sweeney et al., 2006). In their results, 47 patients were included in the intent-to-treat efficacy analysis. Three patients (6.4%) achieved complete responses and 10 (21.3%) partial responses, thus the overall response rate of 27.7%. Ten patients (21.3%) had stable disease and 22 patients (46.8%) progressed. The median time to progressive disease was 2.9 and median overall survival was 9.6 months. Median duration of response was 5.0 months. Of these 47 patients assessable for safety, grade 3 or 4 hematologic events were thrombocytopenia (8.5%; 0.0%), neutropenia (4.3%; 4.3%) and anemia (2.1%; 2.1%), respectively. Other toxicities were grade 4 stomatitis/pharyngitis, sepsis syndrome (1 patient each), and grade 3 fatigue (3 patients) and diarrhea (2 patients) (Sweeney et al., 2006). Thus, they concluded that single-agent pemetrexed is safe and active as second-line treatment of patients with advanced metastatic transitional cell carcinoma of the urothelium. Additional evaluation in the first- or second-line setting in metastatic transitional cell carcinoma of the urothelium is warranted (Sweeney et al., 2006).

Our current study evaluated the efficacy and safety of pemetrexed based regimens on response and safety for patients with metastatic bladder cancer. Our results suggested that in treating 105 patients, pooled RR was 26.7% (28/105) in pemetrexed based regimens. Major adverse effects were neutropenia, anorexia, fatigue, and anemia in pemetrexed based treatment. Two treatment related death occurred in pemetrexed based treatment. Thus, we concluded that pemetrexed based regimens are associated with mild activity and relatively good tolerability in treating patients with metastatic bladder cancer.

References

Babjuk M. et al (2011). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol*, **59**, 997-1008.

Bamias A, Aravantinos G, Deliveliotis C, et al (2004). Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol*, **22**, 220-8.

Dreicer R, Li H, Cooney MM, et al (2008). Phase 2 trial of pemetrexed disodium and gemcitabine in advanced urothelial cancer (E4802): a trial of the Eastern Cooperative Oncology Group. *Cancer*, **112**, 2671-5.

Galsky MD, Mironov S, Iasonos A, et al (2007). Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs,* **25**, 265-70.

Huang XE, Tian GY, Cao J, et al (2014). Pemetrexed as a component of first-, second- and third- line chemotherapy in treating patients with metastatic lung adenocarcinoma. *Asian Pac J Cancer Prev*, **14**, 6663-7.

Liu J, Huang XE, Feng JF (2014). Further study on pemetrexed based chemotherapy in treating patients with advanced gastric cancer (AGC). *Asian Pac J Cancer Prev*, 15, 6587-90.

Lu YY, Huang XE, Cao J (2013). Phase II study on Javanica oil emulsion injection (Yadanzi®) combined with chemotherapy in treating patients with advanced lung adenocarcinoma. *Asian Pac J Cancer Prev*, **14**, 4791-4.

McCaffrey JA, Hilton S, Mazumdar M, et al (1997). Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol*, **15**, 1853-57.

Margulis V. et al (2009). Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer*, **115**, 1224-33.

Munoz JJ, Ellison LM (2000). Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol,* **164**, 1523-5.

Ploeg M, Aben KK, Kiemeney LA (2009). The present and future burden of urinary bladder cancer in the world. *World J Urol*, **27**, 289-93.

Roth BJ, Dreicer R, Einhorn LH, et al (1994). Significant activity of paclitaxel in advanced transitional cell carcinoma of the urothelium: A phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol,* **12**, 2264-70.

Sweeney C, Roth B, Kabbinavar F, et al (2006). Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol*, **24**, 3451-7.

Tian GY, Miu M, Huang XE (2014). Systematic analysis of pemetrexed-based chemoradiotherapy for patients with locally advanced or metastatic esophageal cancer. *Asian Pac J Cancer Prev*, **15**, 8475-8.

von der Maase H, Hansen S, et al (2000). Gemcitabine and cisplatin versus methotrextate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*, **18**, 3068-77.

Wei GL, Huang XE, Huo JG, et al (2013). Phase II study on pemetrexed-based chemotherapy in treating patients with metastatic gastric cancer not responding to prior palliative chemotherapy. *Asian Pac J Cancer Prev*, **14**, 2703-6.

Wu XY, Huang XE, Cao J, et al (2014). A predictive model for evaluating responsiveness to pemetrexed treatment in patients with advanced colorectal cancer. *Asian Pac J Cancer Prev*, **15**, 5941-4.