

## RESEARCH ARTICLE

# Study of Pemetrexed-based Chemotherapy for Patients with Locally Advanced or Metastatic Cancers

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### Abstract

**Purpose:** This study was conducted to observe the efficacy and safety of pemetrexed based chemotherapy in treating patients with locally advanced or metastatic cancers as first-line, second-line or third-line therapy. **Materials and Methods:** From May 2011 to January 2015, we recruited 29 patients with advanced breast cancer, 19 patients with advanced ovary cancer, 17 patients with advanced esophageal cancer, 5 patients with advanced gallbladder cancer, 5 patients with advanced cervical cancer and 1 patient with advanced tongue cancer in Jiangsu Cancer Hospital and Research Institute. All of them were pathologically confirmed and treated with pemetrexed based chemotherapy. After two cycles of treatment, efficacy and safety can be evaluated. **Results:** For pemetrexed based regimens, including 76 patients with 6 kinds of advanced cancer were considered eligible for inclusion. Complete remission represents CR, partial remission represents PR, stable disease represents SD, progressive disease represents PD. Among 29 patients with advanced breast cancer, 4 patients chose pemetrexed based regimens as second-line treatment, 1 of them was PR, the other 3 got SD. The last 25 patients made use of this chemotherapy as third-line treatment, except one patient could not be assessed, 2 of them got PR, 6 of them got SD, the remaining 16 of them finally were PD. 19 patients with advanced ovary cancer, 5 patients used this regimens as second-line treatment, 3 of them got PD, the remaining patients got SD, respectively. The last 14 patients made use of pemetrexed based regimens as third-line treatment, RR (CR+PR) was 28.5%. Among 17 patients with advanced esophageal cancer, 2 patients made use of pemetrexed based regimens as first-line treatment, both of them got PR. 4 of them used this chemotherapy as second-line regimen, except 2 patients could not be assessed, the remaining 2 was PD at last. The last 11 patients was third-line users, RR (CR+PR) was 18.2%. Among 5 patients with advanced gallbladder cancer, pemetrexed based regimens was used in 1 patient as first-line treatment and 1 patient as second-line treatment. The curative effect was SD and PD, respectively. 3 patients accepted pemetrexed based regimens as third-line treatment, 2 of them got PD as results and another was SD. Among 5 patients with advanced cervical cancer, just 1 patient adopted pemetrexed based regimens as first-line treatment, whose curative effect was PR. 2 patients chose this chemotherapy regimens as second-line treatment. Both of them got PD as their consequence. The last 2 patients made use of the regimens as third-line treatment, the effect of them was PD and SD, respectively. The one who with advanced tongue cancer, pemetrexed based regimens was used as second-line treatment, and the consequence was PD. About 71.1% patients experienced bone marrow suppression. Among them, 5 patients reached 4 grade. Other toxicity of pemetrexed were neurotoxicity, fatigue, diarrhea, dysphagia and vomiting. No treatment related death occurred with pemetrexed-based treatment. **Conclusions:** Pemetrexed based chemotherapy has considerable effect in patients with advanced cancers such as breast cancer, esophageal cancer and ovary cancer. More randomly clinical trials are needed to verify the results.

**Keywords:** Based chemotherapy - advanced or metastatic cancer - efficacy and safety.

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### Introduction

Pemetrexed is the first agent approved for the treatment of malignant pleural mesothelioma (MPM). In August 2004, pemetrexed was approved as a second-line, single-agent treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). (Rollins et al., 2005). In this study, the clinical development of pemetrexed in relation to other advanced cancers would be discussed.

Pemetrexed (PMX) is a newly developed multi-targeted anti-folate with promising clinical activity in many solid tumors (Essam et al., 2015). Three enzymes - thymidine nucleoside Acid synthetase (thymidylate synthetase, TS), dihydrofolate reductase glycinamide called formyltransferase DHFR and Amino acid RNA nucleoside acyltransferase (dihydrofolate reductase, ARFT), are involved in terminating cell cycle in S phase. (Giovannetti et al., 2004; Scagliotti et al., 2008). Although

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not the first-line chemotherapy, traditionally. Treatment with pemetrexed based chemotherapy is active and is well tolerated in patients with advanced gastric cancer. (Liu et al., 2014). Pemetrexed at 500 mg/m<sup>2</sup> given every three weeks combined with chemotherapy is associated with moderate response and good tolerability in patients with stage IV colorectal cancer. (Wu et al., 2013). In this study, we analysed the potential efficient and safety of pemetrexed based chemotherapy in treating patients with other advanced cancer such as ovary cancer, gallbladder cancer, breast cancer etc.

Despite advances in prevention, risk factor reduction, early diagnosis and treatment, breast cancer remains a main public health concern, with more than a million new cases diagnosed annually, resulting in >400,000 deaths worldwide (Ferlay et al., 2002; Huang et al., 2004). Based on several analysis of pemetrexed-based chemotherapy in patients with advanced or metastatic breast cancer (Garin et al., 2008; Robert et al., 2011), We hypothesized that pemetrexed originated regimen could be established as an optimal schedule for patients with advanced breast cancer (Fang et al., 2014).

In 2013, it was estimated that there will be 22,240 new cases of ovarian cancer and 14,030 deaths due to this disease in the United States; epithelial ovarian cancer (EOC) represents the leading cause of death from gynecologic malignancies (Siegel et al., 2013). Although surgical resection followed by chemotherapy has been considered standard treatment for more than 30 years, new strategies are needed to improve the tolerability and efficacy of treatment for ovarian cancer. (Vaughan et al., 2011).

Esophageal cancer is the eighth most common cancer type and sixth leading cause of cancer death worldwide, which was responsible for 482,300 new cases and 406,800 deaths in 2008 (Jemal et al., 2011). At present, DNF (Docetaxel, Nedaplatin, 5-Fluorouracil) combination chemotherapy is a useful regimen with relatively minor adverse events and may serve as an effective protocol in patients with unresectable esophageal cancer. (Miyazaki et al., 2015). In spite of this, larger number of patients experienced tumor recurrence after accepted DNF combination chemotherapy.

Nearly 500,000 new cases of cervical cancer are reported worldwide each year, (Parkin et al., 2002) making it the third most common cancer diagnosed among females. Considering that human papillomavirus (HPV)-associated tumors arise years, if not decades, after an initial infection; screening programs are not widely available; and the currently existing vaccines have no therapeutic efficacy, no measurable decline in HPV-associated tumors is expected before 2040 (Hellner et al., 2011). Hence, it is critically necessary to develop a new approach.

Gallbladder cancer is an aggressive tumor. Its incidence varies according to geography. Surgery is the standard treatment for localized stage but there is no standard treatment in metastatic or locally advanced disease. (Abahssain et al., 2010). Rarely reports about pemetrexed-based treatment be used for gallbladder cancer available in Pubmed.

Oral tongue squamous cell carcinoma is one of the

most common malignancies among the males. (Agarwal et al., 2014). The tongue is one of the most important structures in the oropharyngeal deglutition process. Patients with tongue cancers not only have to face a life threatening disease, but have to deal with the impact of the disease and the resulting surgical intervention on their quality of life (QOL) as well. (Agarwal et al., 2014). So far, Platinum doublets studied in phase III trials include cisplatin/5-FU, cisplatin/paclitaxel, and cisplatin/pemetrexed. Platinum chemotherapy in combination with 5-fluorouracil and cetuximab has resulted in the longest median overall survival. (Price et al., 2012). On the basis of inference, pemetrexed-based treatment is also worth a try.

## Materials and Methods

### Patients

Patients eligible for this study were diagnosed with pathologically-confirmed breast cancer, ovarian cancer, esophageal cancer, gallbladder cancer, cervical cancer and tongue cancer who have progressed first or second line chemotherapy or even the surgical treatment. Further inclusion criteria were as follows: Chinese; at least 18 years old; life expectancy over 2 months; to sign an informed consent before treatment; adequate bone marrow (platelets  $\geq 100 \times 10^9$  cells/l, absolute neutrophil count  $\geq 1.5 \times 10^9$  cells/l), hepatic (total bilirubin  $\leq 2 \times$  the upper limit of normal; aspartate transaminase  $\leq 3 \times$  the upper limit of normal). Exclusion criteria were: pregnant or breast-feeding women; with other parts of the malignant tumours. The characteristics of patients were listed in Table 1.

### Treatment

Before chemotherapy, all of the patients enrolled in this study received oral dexamethasone 4.5mg twice on the day before, the day of and the day after each dose of pemetrexed. oral multivitamin formula which contain 400mg of folic acid for 5 days. And Vitamin B12 1000ug was given intramuscularly 1 or 2 days prior to the first pemetrexed dose and repeated every 9 weeks until 3 weeks after the last dose. After premedication, 500mg/m<sup>2</sup> pemetrexed as a 10 minute intravenous infusion combined with or not other chemotherapeutics. When the toxicity is beyond the acceptance of patients or the disease progressed, Cycles should be stopped.

### Assessment

We assessed the disease status by the complete histories, blood cell counts, aspartate aminotransferase, total bilirubin, creatinine, especially computed tomography (CT) scans of chest and abdomen. In particular, complete blood cell count was monitored before and after the chemotherapy. Radiological studies such as magnetic resonance imaging and computed tomography were performed after two cycles of therapy to assess tumor. Complete disappearance of all lesions was defined as CR. Decrease of the lesions compared with the past was defined as PR. The state of the illness maintained stable was defined as SD. And the progress of the disease was defined as PD.

### Toxicity

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) (National Cancer Institute). The most frequent toxicities were bone suppression, occurred in 71.1% patients. 39.4% patients with hepatic dysfunction and 27.6% patients vomited. Other side effects include: fever, infection, nausea, vomiting and neurotoxicity. No death of patients was occurred by pemetrexed during the chemotherapy.

### Results

A total of 76 patients were enrolled in this study between May 2011 to January 2015. 29 patients with advanced breast cancer, 19 of them with advanced ovarian cancer, 17 of them with advanced esophageal cancer, 5 of them with advanced gallbladder cancer, 5 of them with advanced cervical cancer, and the last one with advanced tongue cancer. All of them experienced first, second-line chemotherapy or surgical treatment, but the results were failure or recurrence. In the midst of the 29 patients with advanced breast cancer, 4 of them made use of pemetrexed-based regimen as second-line treatment, 3 of them got SD as results, and the last one got PR. 25 of them chose this regimen as third-line treatment, one of them was unable to assess. 16 patients got PD, SD in 6 and the remaining 2 were PR. Among 19 patients with advanced ovarian cancer, 5 patients used this regimen as second-line treatment, 2 of them got PR, rest of them were PD. The last 14 patients chose pemetrexed-based regimen as third-line treatment, there were 8 patients got PD, SD in 2 patient and 4 got PR. Among 17 patients with advanced esophageal cancer, 2 patients made use of pemetrexed-based regimen as first-line treatment, both of them were PR. 4 patients chose this regimen as second-line treatment, 2 of them were unable to assess their condition. the remaining two got PD. And 11 patients used pemetrexed-based regimen as third-line treatment, PR in 2, 1 got SD and the remaining 8 were PD. Among 5 patients with advanced gallbladder cancer, 1 of them used pemetrexed-based regimen as first-line treatment, SD was the result. Another patient made use of this treatment as second-line treatment, he got PD. The last 3 patients chose pemetrexed-based regimen as third-line treatment, 1 got PD as a result and the other 2 patients got PD. Among 5 patients with advanced cervical cancer, 2 of them used pemetrexed-based regimen as second-line treatment, both of them got PD as results, the last 3 patients chose this regimen as third-line treatment. 1 got SD and 2 got PD. The patient with advanced tongue cancer chose pemetrexed-based treatment after failed the first-line chemotherapy. After two cycles, the patient got PD.

The toxicity contained myelosuppression, abnormal liver function, fever, nausea, vomiting and stomatitis. Bone suppression took place in 71.1% patients and 5 of them reached grade 3/4. No death of patients was occurred related to pemetrexed during the procession.

### Discussion

Robert NJ et al reported a subset analysis of a phase II

study of pemetrexed as first-line chemotherapy in patients with advanced or metastatic breast cancer. Based on 35 evaluable patients, the overall response rate (ORR) was 26% (1 CR and 8 PR), and the clinical benefit rate (CR+PR+ stable disease [SD]  $\geq$  6 months) was 40%. Median progression-free survival (PFS) was 4.1 months (range, <1-22.4). Median overall survival (OS) was 18.9 months (range, <1-27.7). (Robert et al., 2011). There were 28 assessable patients with locally advanced or metastatic breast cancer in our study, the clinical benefit rate (CR+PR+SD) for using pemetrexed-based regimen as second-based chemotherapy was 100%. But for the patients chose this chemotherapy as third-line treatment, the clinical benefit rate was 33.3%.

Two phase II trials of combination pemetrexed/carboplatin in platinum-sensitive patients with recurrent ovarian cancer have been reported, demonstrating overall response rates of 51% (Matulonis et al., 2008) and 33% (Sehouli et al., 2012) with minimal toxicity. Our study enrolled 19 patients with advanced ovarian cancer, the over response rate (CR+PR) was 31.6%.

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% (Seiwert et al., 2007; Katipamula et al., 2008; Jatoi et al., 2010; Li et al., 2011). In our study, the patients with advanced or metastatic esophageal cancer got PR when they made use of pemetrexed-based regimen as first treatment, which demonstrated the early use of pemetrexed could be more effective.

Among 43 patients advanced or recurrent squamous or non squamous cell carcinoma of the cervix, after they had failed one prior chemotherapy regimen, pemetrexed at a dose of 500mg/m<sup>2</sup> every 21 days were treated. Six patients (13.9%) had partial responses (at least a 30% decrease in the sum of longest diameter of target lesions taking as reference the baseline sum longest diameter) with a median response of 7 weeks (range 3-27). Twenty-three patients (53.4%) had stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) and fourteen (32.5%) patients had progressive disease. Median progression-free survival was 10 weeks and overall survival was 35 weeks. (Lorusso et al., 2010). Which reflected that more than half patients obtained effective control by pemetrexed-based treatment.

Just Alberts SR et al reported that 58 patients were included in the phase II study of the maximum tolerated dose (MTD) and efficacy of pemetrexed and gemcitabine in patients with either biliary tract or gallbladder carcinoma. Median age was 61 and median follow-up was 18.2 months. A median of three cycles of treatment was given. Six-month survival was 55% and the median survival was 6.6 months (95% confidence interval 5.4-8.7 months) with a median time to progression of 3.8 months (2.4-5.4). In this study, among the 5 patients with advanced gallbladder carcinoma, none got RR (CR+PR), 2 patients got SD. Despite a number of studies have been conducted about the molecular mechanisms of GBC, there have been no effective prognostic biomarkers for GBC to

guide postoperative treatment (Zhang et al., 2015). By this study, pemetrexed-based regimen can be explored further, enlarging the sample size would be more persuasive.

Treatment of head and neck squamous cell carcinoma (HNSCC) includes surgery, radiation therapy, chemotherapy, targeted therapy, or a combination of treatments. Unfortunately, the outcome of therapy in five years of overall survival for the advanced stages of HNSCC is about 50% and patients often suffer recurrences at the primary site or distant metastases (Leemans et al., 2010).

Therefore, we consider it is potential to further clarify pemetrexed could do benefit to more patients. Pemetrexed is a multitargeted antifolate (Cripps et al., 1999; John et al., 2000; Hanauske et al., 2001; De Gramont et al., 2002; Hochster et al., 2004; Louvet et al., 2004), could involve in folate metabolism, including TS, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide for myltransferase.s (Louvet et al., 2004; Hochster et al., 2004; Atkins et al., 2005). Clinical studies suggested pemetrexed a clear anti-tumor activity in a variety of solid tumors, including lung cancer, breast cancer, pancreatic cancer, ovarian cancer and etc. (Bajetta et al., 2003).

In our study, the most frequent toxicities were bone suppression, occurred in 71.1% patients. 39.4% patients with hepatic dysfunction and 27.6% patients vomited. Few patients took place of neurotoxicity. After chemotherapy and given relevant management, hepatic enzyme and the count of leukocyte and platelet returned to normal. Besides, folic acid and vitamin B12 could reduced the side effects of pemetrexed significantly. Therefore, we can conclude pemetrexed based chemotherapy are good tolerability in treating patients with locally advanced or metastatic cancers.

Generally, this systemic study analysed that pemetrexed based chemotherapy are valid and good tolerability in treating patients with locally advanced or metastatic cancers such as breast cancer, esophageal cancer and ovarian cancer. In addition, the early use of pemetrexed could led to more effective result. Although the sample size of tongue cancer cervical cancer gallbladder cancer were small, we strive to publish this experience and present this as another option in treating those cancers.

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