

## RESEARCH ARTICLE

# A Systemic Analysis on Pemetrexed in Treating Patients with Breast 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 breast cancer as first or second line chemotherapy. **Methods:** Clinical studies evaluating the efficacy and safety of pemetrexed based regimens on response and safety for patients with breast cancer were identified using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. **Results:** In first line pemetrexed based regimens, 10 clinical studies which including 513 patients with advanced breast cancer were considered eligible for inclusion. For second line pemetrexed based chemotherapy, 5 clinical studies which including 281 patients with advanced breast cancer were considered eligible. Systemic analysis suggested that, in all patients, pooled RR was 32.6% (167/513) in pemetrexed based first line regimens, and 13.9% (39/281) in pemetrexed based second line regimens. Major adverse effects were neutropenia, leukopenia, fatigue, and anemia in pemetrexed based first line treatment; and lymphopenia, neutropenia, leukopenia, as well as anemia in second line chemotherapy. One treatment related death occurred with pemetrexed based second line treatment. **Conclusion:** This systemic analysis suggests that pemetrexed based first line regimens are associated with a reasonable response rate and acceptable toxicity, however with low response rate for treating patients with metastatic breast cancer when is used in the second line.

**Keywords:** Pemetrexed - breast cancer

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### Introduction

The incidence and mortality rate of breast cancer increased significantly in China over the last several decades (Yu et al., 2007). It was estimated that 121,269 new cases of breast cancer were diagnosed in China in 2000 and 168,013 in 2005 (Yang et al., 2005). 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).

Now, combined chemotherapy is mostly prescribed in neoadjuvant, adjuvant and in metastatic settings of breast cancer. Although CMF regimen represented the gold standard in the 1970s (Bonadonna et al., 1976), anthracycline-based regimens are the mainstay of adjuvant chemotherapy for early breast cancer since the 1990s (EBCTCG, 2005). When single-agent chemotherapy was used in hormone-resistant metastatic setting, agents considered to be active include cyclophosphamide, phenylalanine mustard, vincristine, vinblastine, methotrexate and 5-fluorouracil. Response rates are ranged from 0-38% (Akram et al., 2012). Pemetrexed has been tested in five phase II trials in locally

advanced or metastatic breast cancer, and has shown an activity of around 30% in advanced breast cancer patients with minimal or no prior chemotherapy. In patients who received prior anthracyclines, response rates of 21% were reported. Responses have also been observed in patients who had been pretreated with anthracyclines, taxanes, and capecitabine. Some studies have suggested that a correlation exists between thymidylate synthase tumor expression with pemetrexed antitumor activity; this attractive hypothesis should be confirmed in further studies (Martin, 2006).

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). Grades 3-4 treatment-related toxicities included: neutropenia (36%), leukopenia (17%), fatigue (14%), and anemia (14%). Grade 1/2 alopecia was seen in 8% of patients (Robert et al., 2011).

Garin A et al reported a subset analysis of a phase II study with pemetrexed and carboplatin in patients with

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locally advanced or metastatic breast cancer. Partial responses (RECIST criteria) were achieved in 27 (54.0%) patients (ORR = 54.0%; 95% CI, 39.3-68.2%). The median response duration was 11.1 months (95% CI, 6.5-14.0 months) and the median time to disease progression was 10.3 months (95% CI, 8.3-14.6 months). CTC hematologic toxicities were grade 3/4 neutropenia (58.0%/28.0%) and grade 3 thrombocytopenia (10.0%) and anemia (18.0%). Two (4.0%) patients had febrile neutropenia, 1 of whom died. No grade 4 non-hematologic toxicities occurred. Grade 3 non-hematologic toxicities were ALT (4.0%) and AST elevation, and edema, fatigue, pruritus, rash/desquamation, and renal toxicity (2.0% each) (Garin et al., 2008).

According to this background, we hypothesize that pemetrexed originated regimen could be established as an optimal schedule for patients with advanced breast cancer.

## Materials and Methods

### Search strategy

We searched PUBMED, by using the following search term: (breast cancer) and (pemetrexed). All clinical studies evaluating the impact of pemetrexed on the response or survival and side effects for breast cancer published in English prior to May 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, combined with gemcitabine, epirubicin 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 breast 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 114 papers relevant to the search words by the end of April, 2014. Via steps of screening the title and

reading the abstract, 10 studies were identified (Amadori D 2013; Ditttrich C 2012; Robert NJ 2011; Martin M. 2009; Paridaens R 2007; Garin A 2008; Llombart-Cussac A 2007; Ma CX 2006) when pemetrexed was in first line chemotherapy, and 5 in second line chemotherapy (Spielmann M 2001; O'Shaughnessy JA 2005; Deng QQ 2013; Llombart-Cussac A 2006; Martin M 2003). 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 Amadori et al. was 26.60%, of Ditttrich T et al. was 19.1% and 32.8%, of Robert et al. was 26%, of Martin et al. was 56%, of Paridaens et al. was 32%, of Garin A et al. was 54%, of Llombart-Cussac A was 17% and 15.6%. Totally, 513 patients were enrolled and 167 patients achieved CR or PR, the pooled response rate thus was 167/513 (32.6%).

When pemetrexed was used in second line chemotherapy, 5 studies included in this study are presented and the short-term outcomes suggested that the response rate of Deng et al. (2013) was 15.8%, of Llombart-Cussac A et al. was 9%, of O'Shaughnessy JA et al. was 8%, of Martin M et al. was 21%, and of Spielmann et al. (2001) was 26%. Totally, 513 patients were enrolled and 167 patients achieved CR or PR, the pooled response rate thus was 39/281 (13.9%). Observation on toxicities: major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity.

## Discussion

Breast 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). 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 locally advanced or metastatic breast cancer patients and shown an activity of around 30% in advanced breast cancer patients with minimal or no prior chemotherapy. In patients who received prior anthracyclines, response rates of 21% were reported. Responses were also observed in patients who had been pretreated with anthracyclines,

taxanes, and capecitabine. Some studies suggested that a correlation could exist between thymidylate synthase tumor expression with pemetrexed antitumor activity (Martin, 2006); 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 (Sudoh et al., 2008). Hematological toxicity was considerable, and thrombocytopenia was the most prominent toxicity. Nadirs of blood counts were observed between days 14 and 16 after lobaplatin administration. The majority of patients experienced grade 4 thrombocytopenia (Jan Welink et al., 1999). 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 drugs, 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. 1 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 first line regimens are associated with reasonable response rate and accepted toxicities, however with low response rate for treating patients with metastatic breast cancer when it is used in the second line.. 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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