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Review

Potential role of pemetrexed in metastatic breast cancer patients pre-treated with anthracycline or taxane

Li-Yan Zhou, Ye-Hui Shi, Yong-Sheng Jia, Zhong-Sheng Tong*

Department of Breast Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China

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Abstract

Objectives: This article reviews pharmacology, pharmacokinetic properties, clinical efficacy, and safety in metastatic breast cancer patients, as well as the predictive biomarkers for outcome of treatment with pemetrexed-based regimens.

Methods: PubMed, Embase, OVID, and the Cochrane Library databases were searched from the beginning of each database without any limitations to the date of publication. Search terms were ''pemetrexed'' or ''LY231514'' or "Alimta", "metastatic breast cancer", and "advanced breast cancer".

Results: There were 15 studies ($n = 1002$) meeting our criteria for evaluation. Eight single-agent trials ($n = 551$) and seven using combinations with other agents ($n = 451$) were identified that evaluated pemetrexed for use in patients with metastatic breast cancer. Response rates to pemetrexed as a single agent varied from 8% to 31%, and with combination therapy have been reported to be between 15.8% and 55.7%. With routine supplementation of patients with folic acid, dexamethasone, and vitamin B_{12}, the toxicity profile of these patients was mild, including dose-limiting neutropenia and thrombocytopenia, as well as lower grades of reversible hepatotoxicity and gastrointestinal toxicity. Expression of thymidylate synthase (TS) and other biomarkers are associated with the prognosis and sensitivity for pemetrexed in breast cancer.

Conclusion: Pemetrexed has shown remarkable activity with acceptable toxicities for treatment of metastatic breast cancer patients. Translational research on pemetrexed in breast cancer identified biomarkers as well as additional genes important to its clinical activity and toxicity. Further research is needed to clarify the role of pemetrexed in breast cancer treatment in order to guide oncologists.

Keywords: Metastatic breast cancer; Chemotherapy; Pemetrexed; Anthracycline; Taxane

* Corresponding author. Tel.: +86 18222824776; fax: +86 022 23340123.
E-mail address: tjtonghang@126.com (Z.-S. Tong).

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Introduction

Breast cancer is the most common malignancy among women and is still a leading cause of mortality in women worldwide.[1] Although impressive improvements have been made in adjuvant therapy with anthracyclines and taxanes, development of drug resistance to these agents in recurrent tumors is common, and a substantial proportion of breast cancer patients will eventually develop metastatic disease.[2–4] In the management of metastatic breast cancer, current goals focus on prolonging survival and maintaining the quality of life by controlling symptoms and minimizing related toxicity.[5] Currently, there is no single standard to guide oncologists in choosing additional chemotherapy for patients with metastatic breast cancer who are refractory to anthracyclines and taxanes.[6] Drug therapy with agents such as capecitabine or ixabepilone is often used, but the response rates to these therapies are low.[7,8] More efficacious and safe chemotherapeutic agents, both for monotherapy and in combination with other agents, are needed to treat this pretreated population of patients with metastatic breast cancer.

Pemetrexed is a multi-targeted antifolate cytotoxic chemotherapy agent that has proven activity in several malignancies, including mesothelioma, lung, breast, colon, pancreatic, gastric, bladder, head and neck, and cervical cancers.[9,10] Pemetrexed has been approved for use in combination with cisplatin for first-line treatment of malignant pleural mesothelioma, as a single agent for advanced non-small-cell lung cancer (NSCLC), and for first-line treatment of nonsquamous NSCLC.[11] It has a manageable toxicity profile that includes dose-limiting neutropenia and thrombocytopenia, as well as lower grades of reversible hepatotoxicity and gastrointestinal toxicity. Studies of pemetrexed have shown that the drug is effective in the treatment of previously treated metastatic breast cancer, and has an acceptable toxicity profile. This paper reviews the pharmacology, pharmacokinetics, clinical efficacy, safety, and role in therapy of pemetrexed in patients with metastatic breast cancer.

Material and methods

Search methods were conducted according to the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines.[12] Medline, PubMed, Embase, OVID, and the Cochrane Library were searched from the beginning of each database without any limitations to the date of publication for relevant articles on human studies published in English. Search terms were ‘‘pemetrexed’’ or ‘‘LY231514’’or “Alimta”, “metastatic breast cancer”, and “advanced breast cancer”. The references of selected articles were also reviewed to identify additional publications. The study subjects should be patients with pathologically proven breast cancer who received pemetrexed containing regimens. Studies that did not provide at least the objective response rate or median survival or survival time were excluded.

Results

There were 15 studies ($n = 1002$) meeting our criteria for evaluation. Eight single-agent trials ($n = 551$) and seven that used combinations with other agents ($n = 451$) were identified that evaluated pemetrexed for use in patients with metastatic breast cancer who had been pretreated with anthracycline and taxane.

Pharmacology

The chemical name of pemetrexed is N-[4-[2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d] pyrimidin-5-yl]ethyl] benzoyl]-1-glutamic acid disodium salt (Fig. 1). It is a multitargeted antifolate agent that interferes with the synthesis of nucleic acids, resulting in a cytotoxic effect on neoplastic cells. Pemetrexed inhibits several enzymes in the *de novo* pathways of pyrimidine and purine biosynthesis which are required for the growth and survival of both normal cells and cancer cells, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT).[13,14] These multiple mechanisms of action may explain the greater potency and broader spectrum of antitumor activity of pemetrexed in preclinical studies compared with other antimetabolites such as fluorouracil, methotrexate, or raltitrexed.[13] Pemetrexed can inhibit colony formation of a variety of chemotherapy-resistant cancer cell lines.

Pharmacokinetic profile

Pemetrexed is administered by an intravenous route only, and it is rapidly eliminated (half-life of 3.5 h and

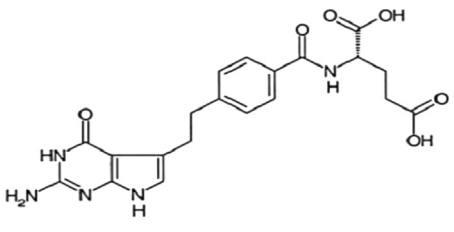

Fig. 1. Structure of pemetrexed.