



## Review article

## Effects of Folic Acid and Vitamin B12 Supplementation on the Efficacy and Toxicity of Pemetrexed in the Management of Advanced Stage Non-Squamous Non-Small Cell Lung Cancer

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### Abstract

Pemetrexed (PMT) is a multi-target antifolate that has been confirmed for the treatment of lung cancer. It has significantly boosted the survival rate of patients with non-squamous non-small-cell lung cancer. Multiple Phase II clinical trials have demonstrated that pemetrexed is an effective monotherapy for a range of solid tumors, including colorectal, breast, neck, and head malignancies. Methods for consolidating pemetrexed with other chemotherapeutics and novel molecularly targeted drugs are currently under investigation. Pemetrexed is currently recommended for first-line dose management with platinum chemotherapies, second-line monotherapy drugs, and, in modern chemotherapy protocols, as continuation therapy following first-line therapy. Vitamin B12 (VB12) and folic acid (FA) supplements can aid to minimize the cytotoxicity of pemetrexed. FA/VB12 has been suggested to have an antagonistic effect on pemetrexed's efficacy. Patients who accept FA/VB12 have a higher tolerance for PMT and a longer lifespan. In this study, the pharmacodynamics, pharmacokinetics, and toxicity of pemetrexed were studied, as well as the implications of FA/VB12 as a co-medication with pemetrexed-based chemotherapy.

**Keywords:** Antifolate, Antimetabolite, Chemotherapy, Folic acid, Pemetrexed, Vitamin B12.

آثار مكملات حمض الفوليك وفيتامين B12 على فعالية وسمية بيمتريكسد في علاج المرحلة المتقدمة من سرطان الرئة ذو الخلايا غير الحشوية غير الصغيرة  
الخلاصة

بيمتريكسد هو مضاد حمض الفوليك متعدد الأهداف يستخدم لعلاج سرطان الرئة. وقد عزز بشكل كبير معدل البقاء على قيد الحياة للمرضى الذين يعانون من سرطان الرئة غير الحشوية غير الصغيرة الخلايا. أظهرت تجارب سريرية متعددة من المرحلة الثانية أن البيمتريكسد هو علاج أحادي فعال لمجموعة من الأورام الصلبة، بما في ذلك الأورام الخبيثة في القولون والمستقيم والثدي والرقبة والرأس. ويجري حالياً التحقيق في طرق دمج البيمتريكسد مع أدوية كيميائية أخرى وعقاقير جديدة موجهة جزئياً. يوصى حالياً باستخدامه ضمن جرعات الخط الأول من العلاجات الكيميائية البلاتينية، وأدوية العلاج الأحادي من الخط الثاني، وفي بروتوكولات العلاج الكيميائي الحديثة، وكعلاج مستمر بعد علاج الخط الأول. يمكن أن يساعد فيتامين B12 وحمض الفوليك في تقليل السمية الخلوية للبيمتريكسد. وقد يكون لفيتامين B12 وحمض الفوليك تأثير مضاد لفعالية بيمتريكسد. المرضى الذين يستخدمون هذه المكملات لديهم تحمل أعلى للبيمتريكسد وعمر أطول. في هذه المراجعة، تمت دراسة الديناميكا الدوائية، والحرارة الدوائية، وسمية البيمتريكسد، بالإضافة إلى الآثار المترتبة على استخدام فيتامين B12 وحمض الفوليك كدواء مشترك مع العلاج الكيميائي القائم على البيمتريكسد.

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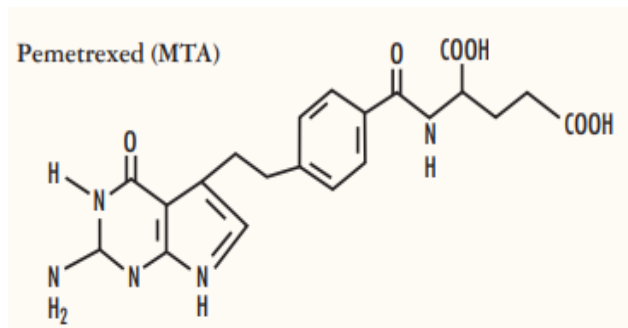
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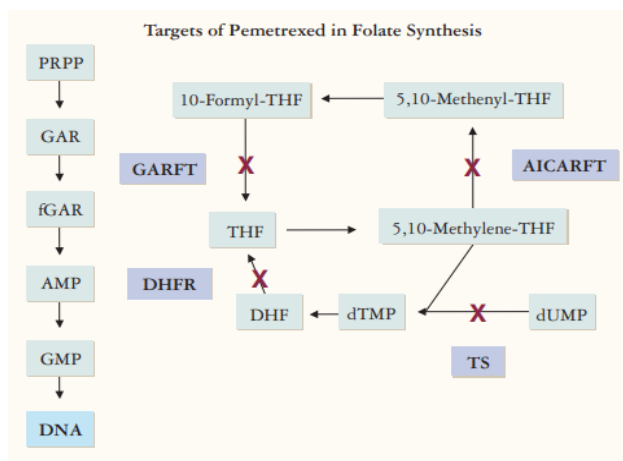
## INTRODUCTION

Antifolate medications, such as 5-fluorouracil or methotrexate, have been regularly used for decades to treat malignant tumors [1]. Folate is necessary for cell division due to its role as a coenzyme in multiple metabolic pathways that lead to DNA synthesis. Folate-dependent processes are therefore necessary for the production of purine and pyrimidine bases, as well as the rapid development of cancer cells [2]. Pemetrexed disodium (PMT) is a pyrrolopyrimidine antifolate that was licensed by the Food and Drug Administration (FDA) of the United States in 2004 [3] (Figure 1).



**Figure 1:** Chemical structure of Pemetrexed [5].

Pemetrexed is a unique anti-folate drug with the capacity to inhibit multiple enzymes, including glycinamide ribonucleotide formyl transferase (GARFT), thymidylate synthase (TS), and dihydrofolate reductase (DHFR) [4,5]. Pemetrexed inhibits the synthesis of precursor purine and pyrimidine nucleotides, hence preventing the formation of DNA and RNA, which are important for the survival and proliferation of normal and malignant cells [6,7] (Figure 2).



**Figure 2:** Schematic illustration of inhibition of multifolate enzymes by pemetrexed [3].

The administration of PMT is facilitated by a reduced folate carrier and a membrane folate binding protein. Once

within the cell, the enzyme folylpolyglutamate synthetase converts pemetrexed into polyglutamate forms rapidly and expertly. Polyglutamate derivatives persist in cells and are more potent TS and GARFT inhibitors [8]. Polyglutamation is a process that happens in malignant cells and normal tissues to a large degree; it is concentration- and time-dependent [8]. Polyglutamated metabolites have a longer intracellular half-life, resulting in a prolonged therapeutic action in cancer cells [8]. Pemetrexed was approved for the treatment of malignant pleural mesothelioma based on the results of a multicenter, randomized Phase III study that demonstrated a survival advantage for the combination of pemetrexed plus cisplatin when compared to cisplatin as monotherapy [9]. Furthermore, pemetrexed is a well-tolerated medication [10] when administered with vitamin B12 and folic acid. The ease of a 10-minute, 500 mg/m<sup>2</sup> infusion, the repeated usage of the prescription (once every three weeks), and the proof that it can be successfully used with other chemotherapies without a considerable dose reduction all contribute to the allure of this compound. In conjunction with cisplatin or carboplatin, this drug is one of the most commonly used first-line treatments for patients with non-squamous lung cancer (NSCLC) because of its efficacy and low-risk profile [3]. This consolidation surpassed a standard regimen (cisplatin/gemcitabine) regarding overall survival (OS) and progression-free survival (PFS). Pemetrexed is frequently recommended for long-term treatment because it increases PFS and OS and is a good option for some patients following first-line therapy [11].

## Pharmacokinetics of Pemetrexed

Pemetrexed can only be administered intravenously, as it is rapidly transported within the body and reaches peak circulation levels within thirty minutes. Approximately 81% of pemetrexed is bound to plasma proteins and eliminated promptly (total systemic clearance: 91.8 mL/min; half-life: 3.5 hours), via glomerular filtration and active tubular secretion. Within 24 hours of dosing, approximately 90% of pemetrexed is removed from the urine, and the remainder is processed in the liver. According to preclinical data, pemetrexed does not interfere significantly with the metabolism of another drug by hepatic enzymes [12,13].

## Toxicity of Pemetrexed

Pemetrexed has a mild toxicity level, and a clinical trial conducted by Scagliotti *et al.* has explored that the main adverse reaction of the drug is a hematologic type of grade 3 or 4. The constitutional side effect of pemetrexed is myelosuppression, which manifests as neutropenia, anemia, thrombocytopenia, mucositis, and skin rash [14]. Furthermore, although the drug has a low emesis risk, nausea, vomiting, and diarrhea have been reported [15]. The altitude of transaminases and bilirubin levels has been

recorded in the number of patients managed with pemetrexed; on the other hand, this increase is ordinarily transitory and asymptomatic [16]. Since pemetrexed is largely eliminated via the renal system, creatinine clearance must be measured before pemetrexed infusion. Patients with creatinine clearance greater than 45 mL/min do not require dose adjustment, but patients with creatinine clearance less than 45 mL/min should avoid pemetrexed because the dosage modification approach is uncertain. In addition, nonsteroidal anti-inflammatory drugs, particularly aspirin, may inhibit the renal clearance of pemetrexed [17].

### **Impact of Vitamin B12 and Folate on Pemetrexed Toxicity**

Vitamin B12 is one of the water-soluble B vitamins that have important metabolic effects on the human body [18]. Vitamin B12 is a cofactor in DNA synthesis, amino acid metabolism, and fatty acid metabolism, according to animal models [19]. Due to its important role in the formation of mature red blood cells in the bone marrow [12], it is regarded as a crucial component for the appropriate functioning of the circulatory system. Folic acid is a precursor to 5,10-methylene-tetrahydrofolate (5,10-CH<sub>2</sub>-THF), which is necessary for purine synthesis via TS and DHFR. Folic acid also functions as a methyl donor in the formation of methionine, which provides a single-carbon moiety for the methylation of cellular activities. Also essential for the methionine cycle is vitamin B12. The methyl-THF produced from 5,10-CH<sub>2</sub>-THF is utilized by VB12 and methionine synthase to convert homocysteine into methionine [20,21]. Supplementation with 1000 mcg of vitamin B12 intramuscularly and 400-1000 mcg of folic acid orally for one week significantly lowers the potentially lethal antifolate toxicities of myelosuppression, diarrhea, and mucositis. The level of pretreatment folate evaluated as plasma homocysteine is a significantly more reliable indicator of patients' functional folate status than red blood cell or serum folate, according to a study published in 2002 [22]. S-adenosylmethionine is the principal source of methyl groups for a variety of key mammalian processes. The methyl group of N<sup>5</sup>-methyltetrahydrofolate (CH<sub>3</sub>FH<sub>4</sub>) is transferred to homocysteine to produce methionine, which is utilized in the synthesis of SAM. In the presence of folate deficiency, plasma homocysteine levels increase, and this is regarded as the most accurate indicator of functional folate status. High homocysteine levels can also be caused by vitamin B6 and vitamin B12 deficiencies. However, vitamin B6 deficiency is uncommon [22]. According to multivariate analyses of early pemetrexed monotherapy trials without vitamin supplementation in search of predictive variables for severe toxicity [22], an elevated plasma homocysteine level was indicative of a folate deficiency and was followed

by a description of more severe adverse effects, such as mucositis, thrombocytopenia, severe diarrhea, and neutropenia. At baseline, homocysteine levels were substantially higher. There was a high correlation between baseline homocysteine levels and fewer thrombocytes and leukocytes on day 8 of treatment cycles [23]. In response to these findings, patients enrolled in pemetrexed clinical trials were given oral folic acid 350-000 µg tablets starting at least 5 days before pemetrexed therapy and continuing for 21 days after the last dose of treatment, as well as intramuscular injections of 1000 µg vitamin B12 every 3 weeks for 3 cycles of pemetrexed administration [22,24]. According to many studies, vitamin supplementation decreases the number of severe adverse medication responses, resulting in an improved pemetrexed therapeutic efficacy and safety profile [25-27].

### **METHODS**

This review article was produced specifically to discuss pemetrexed, as well as its side effects and pharmacokinetics. The current review was arranged by examining the Google Scholar, Research Gate, and PubMed databases for works published between 2000 and 2022 that were derived from desperate articles and studies. Pemetrexed toxicity, pemetrexed therapeutic applications, an antifolate, antimetabolite, vitamin B12, folic acid, folate deficiency, and pemetrexed were used as keywords.

#### **Inclusion criteria**

Inclusion criteria include peer-reviewed journal articles pertinent to antifolate agents; clinical pharmacokinetics of pemetrexed; the use of pemetrexed for advanced stage non-squamous non-small cell lung cancer; vitamin B12 and folic acid effects on pemetrexed efficacy such as clinical trials; review articles; case reports; books; and websites.

#### **Exclusion criteria**

All citations related to pemetrexed nephrotoxicity, pemetrexed resistance mechanisms, pemetrexed effect in other types of cancers, pemetrexed versus methotrexate, and pemetrexed consolidation regimens were excluded.

### **DISCUSSION**

Cancerous cells, particularly epithelial carcinoma, result in the development of several molecular abnormalities; hence, the use of pharmaceuticals that explore their action across multiple routes is likely to be more effective than therapies that aim to target individual pathways [28,29]. Therefore, drug-like pemetrexed with multiple enzyme aims, leading to suppression of purine and pyrimidine integration, would be considered to have a broad range of efficacy. This finding is supported by existing clinical data. Determining that this medicine has a broad spectrum of anticancer efficacy in a vast array of epithelial cancers

[28,29]. Vitamin co-medicine has an acceptable toxicity profile when used. Since pemetrexed is an antifolate medication that competes with natural folates, there is a concern that the addition of VB12 and FA may increase intracellular folate levels and reduce PMT's chemotherapeutic efficacy, although this has not been demonstrated in clinical trials. It has been demonstrated that high dosages of FA and VB12 minimize PMT toxicity and increase PMT efficacy in cases of malignant pleural mesothelioma [30]. However, it remains unknown whether vitamin supplementation affects PMT's effectiveness. Increased levels of natural folates are associated with reduced antifolate drug activity in murine leukemia cells [30]. Pemetrexed undergoes a limited hepatic metabolism. Pemetrexed is not anticipated to have a clinically significant effect on the reduction of the metabolic clearance of drugs metabolized by the cytochrome P450 isozymes CYP3A, CYP2C9, CYP2D6, and CYP1A2. Similarly, no correlation has been established between the levels of liver enzymes SGOT or SGPT or total bilirubin and the pharmacokinetics of pemetrexed. Pemetrexed has not been evaluated in patients with severe hepatic dysfunction [31]. Pemetrexed has demonstrated clinical efficacy against cancers such as mesothelioma. The initial dose (500 mg/m<sup>2</sup>) and treatment should be repeated every three weeks. As previously explained, patients who take vitamin supplements respond well to therapy and see improvements in lung mobility and volume. In addition, these cases demonstrated improvements in the quality of life criteria, including dyspnea, symptom distress, pain, and functional capacity [32,33]. Other reviews of pemetrexed have revealed that the addition of folic acid and vitamin B12 to the therapeutic regimen reduces the overall toxicity [34]. In two-phase II non-small-cell lung cancer research studies, the response rates for pemetrexed monotherapy were 15.8% and 23.3%. Further phase II studies of pemetrexed in chemotherapy-naïve patients with breast [35], pancreatic [36], and colorectal malignancies [27] have demonstrated response rates ranging from 6% (pancreatic cancer) to 31% (colorectal cancer) (breast cancer). In early studies, cutaneous side effects, or rashes, were common and sometimes severe. There was a widespread erythematous maculopapular rash with a predominant trunk distribution. In contrast, the use of preventative corticosteroids has substantially reduced the intensity and frequency of this adverse effect [29]. In terms of extravasation events, Pemetrexed was classed as non-vesicant [37]. This article examines the reasons why malignant cases supplemented with folic acid and vitamin B12 respond better to treatment and have a greater overall survival rate than patients who are not supplemented. Pemetrexed should be used as a cornerstone of consolidation treatment, together with both conventional and innovative anti-cancer medicines.

## Conclusion

Pemetrexed is a several targeted folate analog suppressers that constrain the creation of the two purines and pyrimidines and is effective in numerous solid malignancies. Administration of pemetrexed is simple (10-minute infusion every 21 days) and is related to manageable side effects, principally when taken with vitamin supplements. The efficacy of pemetrexed is not negatively impacted by using vitamin supplementation.

## Conflicts of interest

The authors declare no conflicts of interest.

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## Data sharing statement

N/A

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