Revisiting cutaneous adverse reactions to pemetrexed

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Received March 10, 2011; Accepted July 1, 2011

DOI: 10.3892/ol.2011.352

Abstract. Pemetrexed (Alimta®) is a multitargeted antifolate drug approved as a single agent or in combination with cisplatin for the treatment of a small number of malignancies including advanced and metastatic non-squamous non-small cell lung cancer (NSCLC), and malignant pleural mesothelioma. This review reports the recent peer-reviewed publications and original findings regarding cutaneous adverse reactions (CARs) to pemetrexed. Pemetrexed-related CARs are frequently reported under the unspecific term 'skin rash'. However, more specific diseases were tentatively identified as alopecias, urticarial vasculitis, acute generalized exanthematous pustulosis, toxic epidermal necrolysis, radiation recall dermatitis and pityriasis lichenoides. Most of the skin reactions occur shortly after pemetrexed administration. As with methotrexate-related CARs, the cell cycle arrest in the S phase may be regarded as a direct and major cause of the cytotoxic pathobiology. An adverse immune reaction is unlikely. In conclusion, pemetrexed is responsible for CARs exhibiting a variety of clinical presentations. Their origin is likely attributed to direct cytotoxicity following the cell cycle arrest in the S phase and cell necrosis.

Contents

1. Introduction

Most human lung cancers correspond to non-squamous non-small-cell lung carcinomas (NSCLC). The curative potential of surgery is limited by the disease extension at presentation. In addition, a large group of patients present subsequent relapses. Adjunctive cytostatics are commonly administered including taxoids, paclitaxel and docetaxel, as well as gemcitabine, vinorelbine and irinotecan (1). Cisplatin and other concurrent treatments are commonly administered in combination with these agents to increase the cure rate. More recently, pemetrexed (Alimta®, Eli Lilly and Co., Indianapolis, IN, USA) was introduced with the expectation of improved clinical efficacy in the treatment of human neoplasms including NSCLC (1-4).

A PubMed, Medline and EMBASE search was performed to collect information regarding cutaneous adverse reactions (CARs) to pemetrexed. In addition, personal findings were retrieved from our files.

2. Pemetrexed

Pemetrexed is a multitargeted antifolate compound (Table I) exhibiting a broad spectrum of activity against a number of human neoplastic cell lines (5-8). The drug predominantly inhibits thymidylate synthetase and other folate enzymes (9). These enzymes are involved in the synthesis of purines and pyrimidines, and include dihydrofolate reductase, glycinamide ribonucleotide formyl transferase and 5-amino-4-imidazolecarboxamide ribonucleotide transformylase (10). Similar to many folate-targeted drugs, pemetrexed is a substrate for folylpolyglutamyl synthetase. By targeting various enzymes (11) and other molecular compounds (12), pemetrexed affects the biomolecular synthesis of substrates necessary for cell growth and division. In particular, it causes cell-cycle arrest in the S phase.

Pemetrexed is transported into neoplastic and healthy cells mainly by a reduced folate carrier transport system, and it undergoes rapid intracellular transformation by folylpolyglutamate synthetase into the more potent polyglutamate derivatives (13). Pemetrexed exhibits dose-proportional increases in plasma concentration without signs of accumulation in patients with normal renal function. The drug has a small steady-state volume of distribution of approximately 15 litres and is rapidly eliminated from plasma through urinary excretion with a half-life of 2 to 5 h at doses of 525-700 mg/m^2. Third-space accumulation does not appear to play a clinically prominent role (14). Since pemetrexed is frequently combined with potentially nephrotoxic cisplatin, monitoring of renal function is mandatory. Recommendations for the management

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Key words: pemetrexed, adverse drug reaction, lung cancer, S phase, antifolate drug

Table I. Current antifolate drugs (AFD).

Classical AFD	Non-classical AFD	Multitargeted AFD
Methotrexate	Trimetrexate	Pemetrexed
Raltitrexed	Piritrexim	
Pralatrexate	Nolatrexed	
Lometrexal		
Edatrexate		
Talotrexin		

of pemetrexed toxicity in the presence of renal failure remain to be established, but treatment options with leucovorin, folate, thymidine, carboxypeptidase, or haemodialysis are possible (15). Homocysteine is a marker for overall folate status in the body and was found to predict severe pemetrexed-associated toxicity in a clinical study (16).

In clinical practice, pemetrexed exerts a potent single-agent activity alone or in combination with cisplatin for the treatment of NSCLC and malignant pleural mesothelioma (17-21). Little or no non-cross-resistance is expected between pemetrexed and numerous anticancer drugs. This agent is most likely not involved in resistance in the various multidrug resistance mechanisms (22).

3. Cutaneous adverse reactions

Pemetrexed administration is commonly followed by certain adverse reactions (14,23). These manifestations include myelosuppression (anemia, neutropenia and thrombopenia), and various digestive tract dysfunctions such as nausea, vomiting, diarrhea, constipation, anorexia, stomatitis or oral erosions (24). In oncological practice, the dose-limiting toxicity (DLT) of pemetrexed is determined by its myelosuppression although certain other non-haematological toxicities may occur before myelosuppression is reached.

Pemetrexed-related CARs are commonly referred to as 'cutaneous rash' without any other identification or specificity. In a phase II trial on 59 patients receiving 1 to 12 cycles of pemetrexed therapy (median: 4), 18 patients (31%) experienced grade 3 or 4 cutaneous toxicity (22). Additionally, 2 other patients developed asymptomatic diffuse hyperpigmentation of the upper body that resolved on cessation of treatment. In 2/59 patients (%), CARs led to alteration of the ongoing treatment. Any skin changes completely were resolved on cessation of therapy. Two clinical trials indicated that CARs developed in 17% of patients receiving pemetrexed alone and 22% of patients receiving the pemetrexed-cisplain combination (25).

The non-specific term of cutaneous rash blurs the diversity of clinical and pathobiological events. In some instances, however, CAR identification was more clearly supported (24-32). The specific diseases associated with these events were reported to be alopecia (22), acute generalized exanthematous pustulosis (AGEP) (24), urticarial vasculitis (25), radiation recall dermatitis (RRD) (26-28), toxic epidermal necrolysis (TEN) (29,30), eyelid edema (31) and PL-like dermatitis (32).

The S phase arrest by pemetrexed is known to be a cellular event that exhibits similar effects to methotrexate, another antifolate agent. Certain CARs related to these two cytostatics resemble one another in that the time course of the drug reactions is consistent with a direct drug toxicity. Additionally, no immunological intervention has been demonstrated thus far. Severe CARs described for methotrexate and pemetrexed were variously reported under the name TEN syndrome or TEN-like dermatosis (29,30). Conceptually, the pathobiology of the two conditions may be different (33-40). However, the treatment modalities remain to be determined (38,39).

The case of pemetrexed-induced PL-like dermatitis occurred during the period that patients were administered preventive folate and vitamin B supplementation and a short course of corticotherapy (32). The distinction with regular PL (41-44) is not easily achieved during standard histopathological examination. By contrast, immunohistochemistry revealed certain unusual aspects (32). On the one hand, the Ki67 index was high, exhibiting labelled nuclei of irregular size located over the whole thickness of the epidermis. These features may be related to a block of the cell cycle. On the other hand, the calprotectin (MAC 387) immunolabelling was present throughout the epidermis and appeared notably moth-eaten, indicating severe vacuolar alterations. As observed in other skin disorders (lichen planus, TEN and thermal burns) the MAC 387-positive keratinocytes were presumably metabolically altered and/or engaged in a regenerative phase. The apparently empty cavities corresponded to intracytoplasmic vacuoles as well as intercellular focal widening. The combination of these features was interpreted as sublethal signs. The dermal dendrocyte alterations were reminiscent of the methotrexate-induced changes (45).

The RRD following pemetrexed (25,26) is similar to that related to other cytostatics (46,47). AGEP (48-50) is another condition that has rarely been associated with pemetrexed (24).

In some instances, CARs associated with anti-cancer treatment may be predictive for the efficacy of the drug on the neoplasm (51). Such a characteristic has yet to be evaluated for pemetrexed.

4. Prevention of cytotoxicity

Evidence suggests that pemetrexed inhibits multiple enzyme targets (4). Thus, in experimental settings, the co-administration of thymidine failed to completely reverse pemetrexed-induced cytotoxicity in tumor cell lines. However, the combination of thymidine and a purine source, such as hypoxanthine, resulted in almost 100% reversal of cytotoxicity (22).

In a series of pemetrexed clinical trials, routine administration of folic acid and vitamin B12 was provided, beginning 1 week prior to chemotherapy. This supplementation was intended to improve the 'functional folate status' of patients prior to receiving pemetrexed. Patients with a poor functional folate status, indicated by elevated baseline plasma homocysteine concentrations, experienced worse toxicity with pemetrexed, especially grades 3 and 4 myelosuppression, mucositis and diarrhea [Niyikiza C, *et al*: LY231514 (MTA): relationship of vitamin metabolite profile to toxicity. ASCO 17: 1558, abs. 2139, 1998]. The oral folic acid and

intramuscular vitamin B12 supplementation has been found to significantly decrease the incidence of these toxicities and the drug-related fatal myelosuppression [(23) and Bunn P, *et al*: Vitamin B12 and folate reduce toxicity of Alimta™ (pemetrexed disodium, LY231514, MTA) a novel antifolate/antimetabolite. ASCO 20: 76, abs. 300, 2001].

Dexamethasone 2x4 mg daily for 3 days preceding and the day following pemetrexed administration is thought to prevent certain adverse reactions to pemetrexed (22).

5. Conclusion

Pemetrexed is responsible for a high prevalence of CARs. Preventive measures including folic acid and vitamin B supplementation, and high-dose dexamethasone administration likely reduce both the prevalence and severity of CARs [(23) and Bunn P, *et al*: Vitamin B12 and folate reduce toxicity of Alimta™ (pemetrexed disodium, LY231514, MTA) a novel antifolate/antimetabolite. ASCO 20: 76, abs. 300, 2001]. Nonetheless certain severe CARs remain possible.

The unspecific term 'skin rash' used to report pemetrexed-associated CARs appears unsatisfactory. The skin lesions should be more clearly defined and identified. This is true for any other CAR induced by anti-neoplastic drugs such as the anti-epidermal growth factor receptors (anti-EGFR) (52,53).

In the case of pemetrexed-related CARs, lesions are or simulate specific, often drug-related dermatoses. In this context, it is important to distinguish the result of direct cytotoxic effects from an indirect immune reaction. The clinical and the regular histopathological assessments may fail to make the distinction. Immunohistopathology may provide certain clues to elucidate the problem. By gathering information, new preventive measures may be offered to the clinicians.

Antifolate resistance may reduce CAR severity. This process potentially results from impaired cell influx or increased efflux, impaired polyglutamation, increased expression or mutation of cellular targets, or the intracellular accumulation of tetrahydrofolate cofactors.

Pemetrexed is approved for the first-line treatment of non-squamous-cell lung cancer, second-line treatment of NSCLC, and first-line treatment of malignant pleural mesothelioma. The drug has substantially added to the clinical importance of antifolates in oncology. Adverse reactions include myelosuppression, various digestive tract dysfunctions and a number of CARs inappropriately referred to as 'skin rashes'. The pathobiology of these reactions is likely to be related to a direct cytotoxic effect of the drug on the epidermal and endothelial cells without a primary intervention of the immune system.

The recognized CARs to pemetrexed comprise lesions closely resembling diseases where keratinocytes and/or endothelial cells are altered in their integrity and viability. Thus, the clinical presentation may closely resemble certain dermatoses unrelated to cytostatics, instead of dermatoses correlated to immune disorders or to drug-induced reactions related to toxic metabolites. When the pathobiology is uncovered, the choice of preventive and curative measures regarding antifolate-related CARs should be more fully appreciated. The drug dosage and rhythm of administration, as well as renal function, are crucial parameters that should be considered and examined.

Acknowledgements

This work was supported by a grant from the 'Fonds d'Investissement de la Recherche Scientifique' of the University Hospital of Liège. No other sources of funding were used to assist in the preparation of this manuscript. The authors appreciate the excellent secretarial assistance of Mrs. Ida Leclercq.

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