Pemetrexed in the treatment of thoracic malignancies: a single centre experience in Singapore

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ABSTRACT

Introduction: This study aimed to examine the efficacy and toxicity of pemetrexed in Singapore.

Methods: We conducted a retrospective review of patients treated with pemetrexed between July 2005 and November 2007. RECIST was used to assess the efficacy independent of the treating physician's assessment, and NCI CTC-AE version 3.0 was used to describe adverse events.

Results: 37 patients had non-small-cell lung cancer (NSCLC) and six had malignant pleural mesothelioma. Those with NSCLC had a median age of 60 and an ECOG PS of 0–1, and they were predominantly male, ethnic Chinese and smokers. A median of two cycles were delivered (total 95; range 1–12). Grade 3/4 toxicity was rare. Five (14 percent) patients had an objective response (one complete, four partial) and 13 (35 percent) had stable disease. Median time to treatment failure was 1.86 months (95% confidence interval [CI] 0–6.5). Median overall survival was 18.6 months (95% CI 12.6–27.7). Median age of patients with mesothelioma was 46.5 (range 29–73) years. Five men and one woman received a median of four (total 30, range 1–15) cycles of pemetrexed in combination with cisplatin. Three patients had a partial response, two had stable disease and one had disease progression. Grade 3/4 toxicities were as follows: leucopenia, neutropenia and thrombocytopenia in one patient.

Conclusion: The results of this retrospective study and literature review show that pemetrexed is safe and efficacious in the treatment of Asian patients with NSCLC and mesothelioma.

Keywords: Asian, Chinese, efficacy, pemetrexed, toxicity

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INTRODUCTION

Pemetrexed (Alimta™, Eli Lilly and Company, Indianapolis, IN, USA) is a novel folate analogue. The agent is metabolised intracellularly to polyglutamated forms, which along with pemetrexed, inhibit the folate-requiring enzymes dihydrofolate reductase, thymidylate synthase (TS) and glycinamide ribonucleotide formyltransferase, thus inhibiting the *de novo* synthesis of thymidine and purine nucleotides.[1] North American and European regulatory agencies have approved pemetrexed in combination with cisplatin (Bedford Laboratories, Bedford, OH, USA) for the treatment of patients with malignant pleural mesothelioma who have unresectable disease or are not otherwise candidates for curative therapy, and as the single agent for the therapy of previously treated patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC).[2-4]

Ethnic differences exist in the metabolism and pharmacokinetics of anticancer drugs that can modulate their activity and toxicity in different populations.[5] In the treatment of NSCLC, the most commonly cited example is docetaxel (Taxotere™, Sanofi Aventis, Paris, France). At doses commonly used for Caucasians, Asian patients have greater rates of neutropenic fever and other haematologic toxicities, while developing less fluid retention. This has been explained in part by the presence of genetic polymorphisms.[6] While Asian medical centres participated in clinical trials that confirmed the efficacy and safety of pemetrexed in the treatment of malignant mesothelioma and NSCLC, limited data from these studies has been published concerning the side effect profile and activity of pemetrexed in patients of Asian ethnicity until recently.[7-10] Moreover, to the best of our knowledge, there have not been any published studies that assessed the use of pemetrexed in Asian patients outside of Japan when we started this project.

We aimed to help fill this gap by providing an estimate of the safety and activity of pemetrexed in Asian patients via a retrospective review of our experience at the Johns Hopkins Singapore International Medical Centre. We also performed a review of the literature

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Table I. Baseline characteristics and treatment delivery of patients with non-small-cell lung cancer (n = 100).

Characteristic	No. (%)
Median age; range (yrs)	60; 45–89
Gender	
Male	29 (78)
Female	8 (22)
Ethnicity	
Chinese	32 (86)
Arab	2 (5)
Malay	1 (3)
Indian	1 (3)
Vietnamese	1 (3)
Smoking status	
Smoker	22 (59)
Never smoked	15 (41)
Pathologic diagnosis	
NSCLCA-NOS	19 (51)
Adenocarcinoma	12 (32)
Squamous cell	4 (11)
BAC	1 (3)
Large cell cancer	1 (3)
ECOG performance status	
0–1	29 (78)
2	8 (22)
Site of metastasis	
Bones	15 (41)
Pleura	9 (24)
CNS	7 (19)
Lung	7 (19)
Adrenal	4 (11)
Skin	1 (3)
Prior therapy	
At least one	37 (100)
Median no.; range	1; 1–4
Prior systemic treatment	
Carboplatin/gemcitabine	21 (57)
Carboplatin/irinotecan/paclitaxel	9 (24)
Gefitinib	9 (24)
Carboplatin/paclitaxel	6 (16)
Erlotinib	2 (6)
Cisplatin/gemcitabine	1 (3)
Cisplatin/etoposide	1 (3)
Carboplatin/docetaxel	1 (3)
Paclitaxel	1 (3)
Radiation	18 (49)
No. of pemetrexed cycles received	
Total	95
Median no. ; range	2; 1–12

NSCLCA: non-small-cell lung cancer; NOS: not otherwise specified; BAC: bronchoalveolar carcinoma; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system

and presented a comprehensive discussion on the use of pemetrexed in Asian patients.

METHODS

We conducted a retrospective review of patients treated with pemetrexed with palliative intent at the Johns Hopkins Singapore International Medical Centre between July 2005 and November 2007. All patients who received pemetrexed and had a diagnosis of NSCLC or malignant pleural mesothelioma were identified through our pharmacy records and included in the analysis. Medical records were extracted, and data on age, ethnicity, gender, performance status, smoking history, the medications given and their doses, and specific pathologic sub-types were recorded. Non-smokers were defined as patients who had smoked < 100 cigarettes in their lifetime or former light smokers (those who had stopped smoking for at least 15 years and had a total of ≤ 10 pack-years of smoking). All available radiologic and laboratory data were reviewed.

The Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 was used to assess the efficacy independent of the treating physician's assessment (modified criteria were used for patients with mesothelioma).[11] The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTC AE v 3.0) (Bethesda, MD, USA) was used for the description of adverse events.[12] The primary endpoint of this retrospective review was the objective response rate, and the secondary endpoints were toxicity, time to treatment failure and overall survival. Descriptive statistics were used to present the baseline demographic and clinical data. Time to treatment failure was defined as the period between the first treatment with pemetrexed and either tumour progression, death, loss to follow-up or toxicity leading to drug discontinuation. Overall survival was measured between the date of first treatment with pemetrexed and the date of death. The overall response rate (complete plus partial response) was estimated with exact 95% confidence interval (CI). Time-to-event endpoints were estimated by the Kaplan-Meier method with corresponding 95% CI.

The institutional review board granted exemption from obtaining informed consent in retrospective studies with de-identified patient data. A literature search was performed using PubMed, Google Scholar, the Johns Hopkins University Welch Medical Library, and by manually searching meeting proceedings for the annual meetings of the American Society of Clinical Oncology and the European Society of Medical Oncology. Representative studies were extracted and discussed.

RESULTS

A total of 43 patients received pemetrexed, out of which 37 had NSCLC and six had malignant mesothelioma. Patients with NSCLC had a median age of 60 (range 45–89) years, and were predominantly male (29 men vs. 8 women), ethnic Chinese (n = 32) and smokers (n = 22). Histology revealed that 19 patients had NSCLC, 12 had adenocarcinoma, four had squamous cell carcinoma, and one patient each had bronchoalveolar and large cell carcinoma. Upon diagnosis, 24 patients had stage IV, 12 had stage III and one had stage II NSCLC. All patients

Table II. Adverse events in patients with non-small-cell lung cancer (n = 37).

Adverse event	No. (%)		
	Any grade	Grade 1/2	Grade 3/4
Haematologic event			
Anaemia	13 (35)	10 (27)	3 (8)
Leucopenia	4 (11)	4 (11)	1 (3)
Neutropenia	2 (6)	1 (3)	1 (3)
Thrombocytopenia	2 (6)	1 (3)	1 (3)
Non-haematologic event			
Fatigue	7 (19)	7 (19)	-
Skin rash	3 (8)	3 (8)	-
Nausea	2 (6)	2 (6)	-
Vomiting	1 (3)	1 (3)	-
Hiccups	1 (3)	1 (3)	-
Mucositis	1 (3)	1 (3)	-
Anorexia	1 (3)	1 (3)	-
Constipation	1 (3)	1 (3)	-
Pneumonia	2 (6)	-	2 (6)

had received at least one prior regimen of systemic treatment (median 1, range 1–4). The details of these prior regimens are presented in Table I. 29 patients had an Eastern Cooperative Oncology Group Performance Status Scale (ECOGPS) of 0 or 1. (Table I)

The patients received a median of two cycles of treatment (total 95, range 1–12). All patients received an initial dose of 500 mg/m^2 and pre-medication with vitamin B_{12} and folate. Two patients had a dose reduction to 450 mg/m^2, two received concomitant treatment with bevacizumab and another two with cetuximab. Grade 3/4 adverse events were anaemia (n = 3), pneumonia (n = 2), neutropenic fever (n = 1) and thrombocytopenia (n = 1). Grade 1/2 toxicities are depicted in Table II. There were no deaths attributable to pemetrexed. Five (14%) patients had an objective response (one complete and four partial responses) and 13 (35%) had stable disease. The median time to treatment failure was 1.86 months (95% CI 0–6.5). The median overall survival was 18.6 months (95% CI 12.6–27.7). These results are summarised in Table III.

The median age of patients with mesothelioma was 46.5 (range 29–73) years. Three patients had stage III and another three had stage IV mesothelioma at diagnosis. Five men and one woman (four ethnic Chinese, one Indian and one Arab) received a median of four cycles (total 30, range 1–15) of pemetrexed in combination with cisplatin. One patient had received prior therapy with cisplatin and gemcitabine. One patient had a dose reduction of pemetrexed to 450 mg/m^2. Three patients had a partial response, two had stable disease and one had progressed at the time of first evaluation. Grade 3/4 toxicities were as follows: one patient had leucopenia, neutropenia and thrombocytopenia. Grade 1/2 adverse events were anaemia (n = 4); fatigue (n = 2), anorexia (n = 2), nausea (n = 2) and fever without neutropenia (n = 1). With a median actual follow-up of 12 months, time to treatment failure was 2.8 (range 0.7–7.4) months, and the median overall survival had not been reached.

Table III. Efficacy of pemetrexed in non-small-cell lung cancer (n = 37).

Response	No. (%)	95% CI
Complete (CR)	1 (3)	0–8
Partial (PR)	4 (11)	1–21
Stable disease	13 (35)	20–51
Progressive disease	19 (51)	35–67
Objective response rate (CR + PR)	5 (14)	3–25

CI: confidence interval

DISCUSSION

This retrospective review shows that pemetrexed appears to be as effective and safe in the treatment of Asian patients as it is in the treatment of Caucasians. 14% of patients with NSCLC had an objective response and 35% had stable disease. The median time to treatment failure was 1.86 months (95% CI 0–6.5), while the median overall survival was 18.6 months (95% CI 12.6–27.7). 19% of patients had Grade 3 or 4 adverse events. In the smaller group of patients with malignant pleural mesothelioma, three partial responses and two stable diseases were seen, with only one progression at first response evaluation. No unexpected toxicity, including death attributable to pemetrexed, was seen. As most of the patients were classified as having NSCLC not otherwise specified (and only four had squamous cell cancer), the authors decided not to perform an analysis of survival relating to histology.

These results are similar—with all the caveats of comparing our small single-centre, retrospective series with large multi-centre randomised studies—to those seen with pemetrexed in phase III trials in NSCLC and malignant pleural mesothelioma. In the trial by Hanna et al, 9.1% of patients with NSCLC had partial responses and 45.8% had stable disease. Their median time to treatment failure was 2.3 (range 0–18.2) months and the median overall survival period was 8.3 months.[8] In a study by Vogelzang et al, the objective response rate for patients with malignant pleural mesothelioma who received pemetrexed in combination with cisplatin was 41%. The median overall survival was 12.1 months and the median time to tumour progression was 5.7 months (time to treatment failure was not fully reported).[7]

A study presented at the 2007 annual meeting of the

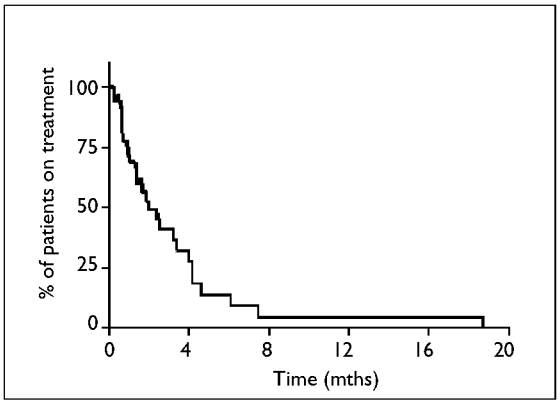

Fig. 1 Line graph shows time to treatment failure.

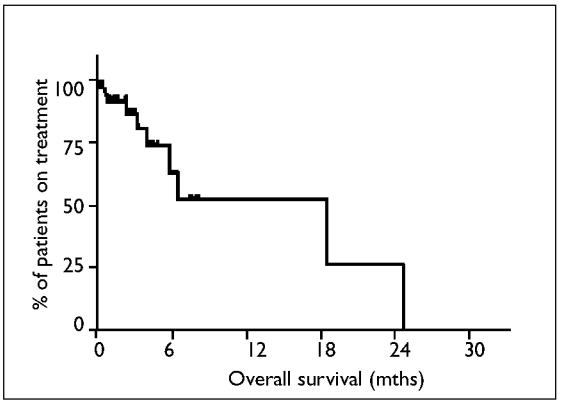

Fig. 2 Line graph shows the overall survival of the patients.

American Society of Clinical Oncology reported that the safety and efficacy of pemetrexed in non-Caucasian and Caucasian patients is similar. However, in this pooled analysis of five clinical trials, the non-Caucasian group also included patients of African descent and Hispanic patients, thus confounding its results.[13] A phase I study conducted in Japanese patients reported that pemetrexed is safe in doses up to 1,000–1,200 mg/m^2, and that responses were seen in patients with NSCLC.[14] Moreover, in a multi-centre phase II trial in Japan, in which 244 patients were randomised to receive pemetrexed at doses of 500 mg/m^2 or 1,000 mg/m^2, the median survival time exceeded 12 months (in second- and third-line settings).[15]

Recently, the results of a retrospective analysis of an East Asian sub-group in a large randomised phase III trial comparing pemetrexed or gemcitabine in combination with cisplatin in the first-line treatment of patients with NSCLC[9] showed that results for patients from Taiwan and South Korea (n = 126) compared favourably to non-Asian patients (n = 1,725 for the complete study population). The overall survival for Asian patients who received pemetrexed and cisplatin was 17.1 vs. 16.5 months for those treated with gemcitabine and cisplatin (the difference was not statistically significant), which was considerably higher than the 10.3 months seen in the intention-to-treat analysis for both arms in the overall study population. These results are even more impressive as the analysis took into consideration only patients with non-squamous histology (median survival 21.2 vs. 17.7 months for Asian patients, favouring the pemetrexed-containing arm, with hazard ratio (HR) 0.7 and 95% CI 0.39–1.24). The results for progression-free survival in the same study also showed an advantage for pemetrexed in East Asian patients. The median progression-free survival was 6.4 months for patients who received cisplatin and pemetrexed vs. 5.6 months for those treated with cisplatin and gemcitabine (HR 0.61, 95% CI 0.39–0.96).[9]

Another prospective multi-centre study conducted in Korea evaluated the efficacy and safety of pemetrexed in Korean patients with advanced NSCLC who had prior chemotherapy.[10] The overall response rate for 78 evaluable patients was 5.1% (95% CI 1.4–12.6; partial response 4/78; no complete response). The disease control rate, including complete response, partial response and stable disease was 46.2% (36/78, 95% CI 34.8–57.8). With a median 8.7 months follow-up, the median time to progression was 3.1 months (95% CI 1.17–5.03) and the median overall survival was 7.8 months (95% CI 5.19–10.35). The median overall survival for patients with adenocarcinoma histology was 18.7 months compared to 6.1 months for non-adenocarcinoma. In a multivariate analysis, the ECOGPS 0–1 (HR 0.331, 95% CI 0.135–0.814) and adenocarcinoma (HR 0.504, 95% CI 0.283–0.899) were independent factors for prolongation of overall survival.

Based on the results of a recent phase III randomised clinical trial, it is now clearly recognised that histology is a strong predictive factor for outcomes (overall survival and progression-free survival) using pemetrexed[21] and that the US Food and Drug Administration has amended its approval for use only in patients with non-squamous NSCLC. This phenomenon can been seen in both the first-line setting and in the maintenance treatment setting[17,18] for lung adenocarcinoma. The reason for this differential efficacy has not yet been completely elucidated; one plausible explanation relates to the expression of TS in lung cancer cells.[19] Preclinical data suggests that over-expression of TS correlates with lower sensitivity to pemetrexed, partially explaining the lack of significant benefit from pemetrexed in squamous cell carcinoma as well as in small cell carcinoma, which are the two tumour types associated with high TS expression in contrast to adenocarcinoma.[20-24] In malignant pleural mesothelioma, Japanese investigators have presented

a phase I/II trial of pemetrexed in combination with cisplatin, in which 500 mg/m^2 of pemetrexed could be given safely with 60 mg/m^2 of cisplatin every three weeks. The response rate was 36.8% with the doublet.[16]

In conclusion, despite its relatively small sample size and retrospective nature, our study, along with this literature review, suggests that pemetrexed is safe and efficacious in Asian patients with NSCLC and malignant pleural mesothelioma.

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