DE GRUYTER OPEN

HeSMO • 6(2) • 2015 • 14–18
DOI: 10.1515/fco-2015-0008

Forum of Clinical **Oncology**

Efficacy and Toxicity of Maintenance Pemetrexed Following Induction Treatment with Pemetrexed Plus Cisplatin for Advanced Non-small-cell Non-squamous Carcinoma of the Lung

Kim DH, Kinmond A, Gilani S, Giridharan S, Jegannathen A.

The University Hospital of North Staffordshire.
Princes Road, Stoke-on-Trent, Staffordshire ST4 7LN.

Abstract: INTRODUCTION: The aim of this study is to assess the efficacy and toxicity of maintenance pemetrexed following induction treatment with cisplatin and pemetrexed for patients with advanced non-small cell lung cancer.

PATIENTS AND METHODS: Eligible patients following four cycles of intravenous pemetrexed (Alimpta©; 500 mg/m^2) and intravenous cisplatin (75 mg/m^2) were given 21-day cycles of maintenance pemetrexed (500 mg/m^2) until disease progression, unacceptable adverse event or death. From a total 80 patients receiving palliative induction chemotherapy, 17 subsequently received maintenance pemetrexed.

RESULTS: The mean number of maintenance cycles completed was 5.9 (range 1–20; median 3.0). The mean progression-free survival (PFS) was 5.2 months (range: 2–15; median: 2.0) and the 1-year PFS was 17%. Treatment was discontinued due to disease progression (71%), adverse event (21%) and death from study disease (7%). Grade 3–4 laboratory and non-laboratory adverse events were seen in 11.8 and 17.6% of patients, respectively. Anaemia was the most common adverse event (71% of all patients; 65% grade 1–2; 5.9% grade 3–4). The most common reason for withdrawal due to adverse event was declining renal function. There was a statistically significant correlation between worsening performance status and reducing number of maintenance cycles completed (Spearman's rank; $R = -0.511$, $p = 0.036$).

DISCUSSION: The median PFS was lower than in previous studies with a higher than previously reported frequency of adverse events. Clinicians must monitor renal function and full blood counts vigilantly, especially in patients with performance status greater than 0.

Keywords: *Pemetrexed • Maintenance Pemetrexed • Cisplatin • Advanced lung cancer • non-small cell • non-squamous • Efficacy and Toxicity*

Introduction

Primary lung cancer is the leading cause of cancer-related death worldwide with an estimated 1.6 million new cases diagnosed each year [1, 2]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers and unfortunately, over two-thirds of these will have locally advanced or metastatic disease at diagnosis [3,4].

In patients with metastatic NSCLC of non-squamous histology, current guidelines recommend the combination of cisplatin and pemetrexed as first line induction treatment [5]. Use of platinum-based chemotherapy beyond 4–6 cycles is not recommended due to increased toxicity [2].

The antimetabolite pemetrexed has been advocated by the National Institute for Health and Clinical Excellence (NICE) for ongoing maintenance treatment in responsive locally advanced or metastatic non-squamous NSCLC following induction treatment with a platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel [6]. More recently, the phase III PARAMOUNT study has shown improved PFS and overall survival (OS) compared to placebo in patients treated with continuation maintenance pemetrexed following four cycles of pemetrexed and cisplatin combination first-line treatment [7, 8].

The aim of the current study is to analyse efficacy and toxicity data for all patients receiving pemetrexed continuation maintenance treatment following pemetrexed and cisplatin induction at a large UK-based cancer centre.

* *E-mail: Daniel.kim@nhs.net*

Patients and Methods

All patients receiving maintenance pemetrexed for NSCLC at The University Hospital of North Staffordshire NHS Trust between March 2012 and April 2014 were retrospectively analysed via inspection of electronic patient records. Primary outcome measures were PFS and total number of maintenance cycles completed. Secondary outcome measures focussed on adverse events and need for acute hospital intervention.

Patients were eligible for the study if they had a diagnosis of NSCLC of non-squamous histology, had locally advanced or metastatic disease at diagnosis, had been treated with a combination of pemetrexed and cisplatin as first-line treatment for four cycles and had no evidence of disease progression after those four cycles. Patients were excluded if they had received any other surgical, radiotherapy or chemotherapy-based treatment prior to commencing pemetrexed and cisplatin chemotherapy.

Induction treatment consisted of four cycles of intravenous pemetrexed (Alimpta©; 500 mg/m^2) and intravenous cisplatin (75 mg/m^2) on day 1 of a 21-day cycle. Radiological progression was assessed via CT scan using the response evaluation criteria in solid tumours (RECIST 1.0) [9]. Maintenance treatment consisted of continuous cycles of intravenous pemetrexed (500 mg/m^2) on day 1 of 21-day cycles plus best supportive care. All patients were given prophylactic dexamethasone and ondansetron prior to pemetrexed infusion in addition to daily folic acid and hydroxycobalamin (Vitamin B12) every 3rd cycle. Maintenance cycles were discontinued in the event of disease progression, unacceptable adverse events or clinical decision. Patients were followed up until death from study disease, discontinuation of maintenance chemotherapy or the close of study dates.

Patients received a CT scan to identify disease progression at least every three cycles or sooner if clinically indicated. Adverse events were evaluated between each maintenance cycle at outpatient clinic appointments and were recorded via the Common Terminology Criteria for Adverse Events version 3.0 [10]. Electronic hospital records were scrutinised and all unplanned admission were evaluated specifically noting the need for blood transfusions and administration of granulocyte colony stimulating factor (G-CSF). In addition, all lab results were evaluated in order to record any renal or haematological toxicity.

PFS was measured from the date of first pemetrexed maintenance dose. Survival analysis was performed using the Kaplain–Meier method. Spearman's rank correlation coefficient was used to analyse the relationship between performance status and number of completed pemetrexed cycles.

There were no human or animal rights concerns and all work was conducted in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and its later amendments.

Results

There were a total of 384 NSCLC diagnoses within the study period, of which 80 received pemetrexed-based combination induction chemotherapy. After exclusions, 17 of these patients received maintenance pemetrexed and were included in this study. Exclusions included disease progression, unfavourable performance status and a history of other surgical, radiotherapy or chemotherapy treatment. Additionally, some patients chose not to continue with treatment.

Patient demographics are detailed in table 1. The mean baseline estimated glomerular filtration rate prior to the first maintenance dose of pemetrexed was 84 ml/min (range: 59 to > 90 ml/min).

Tumour assessment following induction treatment was classed as 'partial response' in 70.6% (n = 12) and

Table 1. Patient and disease characteristics. Figures are number of patients (%). *Where clinicians indicated performance status of 0/1 or 1/2 this has been rounded up to the nearest whole number.

Gender	
Male	6 (35%)
Female	11 (65%)
Age at induction (years)	
Median (range)	67 (54–78)
Mean	65
ECOG performance status*	
0	10 (59%)
1	5 (29%)
2	2 (12%)
Disease stage at diagnosis	
3A	3 (18%)
3B	4 (24%)
4	10 (59%)

'stable disease' in 29.4% (n = 5). The mean number of maintenance cycles given was 5.9 (range 1–20; median 3.0). The mean PFS was 5.2 months (range: 2–15; median: 2.0) and the 1-year PFS was 17% (figure 1).

There was a statistically significant correlation between Eastern Cooperative Oncology Group (ECOG) performance status [11] and number of maintenance cycles completed (Spearman's rank; R = −0.511, p = 0.036) as shown in figure 2.

At the close of the study in March 2014, 18% of patients (n = 3) were still receiving maintenance. Treatment was discontinued due to disease progression in 71% (n = 10), adverse event in 21% (n = 3) and death from study disease in 7% (n = 1) of patients. Possibly, treatment-related adverse events can be seen in Table 2.

Grade 3–4 laboratory (haematological and biochemical) and non-laboratory adverse events were seen in 11.8% and 17.6% of patients, respectively. Anaemia was the most common adverse event (71% of all patients; 65% grade 1-2; 5.9% grade 3-4). Neutropaenia was seen in 41% of patients (grade 1–2: 35.3%; grade 3–4: 5.9%). Patients were withdrawn due to declining renal function in 11.8% (n = 2) of cases.

A total of 47% of patients (n = 8) received emergency hospital assessment during their maintenance pemetrexed treatment. A total of 35% of the study population required a blood transfusion, receiving an average of 2.8 units of packed red cells. A total of 18% of patients (n = 3) required G-CSF in response to neutropaenia.

Post-discontinuation treatment consisted of erlotinib (24%; n = 4), Denosumab (6%; n = 1) and Abraxane (6%; n = 1). Palliative radiotherapy was subsequently used in 29% of patients (n=5).

Table 2. Adverse events possibly related to maintenance pemetrexed administration. Figures are number of patients (%). Grading as per the Common Terminology Criteria for Adverse Events, version 3.0. *Glomerular Filtration Rate.

	All grades	Grade 3, 4 and 5
Laboratory adverse events	*14 (82%)*	*2 (12%)*
Anaemia	12 (71%)	1 (6%)
Renal (GFR*)	8 (47%)	0
Neutropaenia	7 (41%)	1 (6%)
Non-laboratory adverse events	*14 (82%)*	*3 (18%)*
Fatigue	7 (41%)	1 (6%)
Nausea and Vomiting	5 (29%)	1 (6%)
Infection with normal or G1–2 neutrophils	5 (29%)	3 (18%)
Watery eyes (epiphora)	2 (12%)	0
Oedema	2 (12%)	0
Infection with grade 3/4 neutrophils	1 (6%)	1 (6%)
Headache	1 (6%)	0
Malaise	1 (6%)	0
Diarrhoea	1 (6%)	1 (6%)
Constipation	1 (6%)	0
Taste alteration (dysgeusia)	1 (6%)	0
Deep vein thrombosis	1 (6%)	1 (6%)
Pleural effusion	1 (6%)	0
Pneumonitis	1 (6%)	1 (6%)
Hypertension	1 (6%)	0
Emergency hospital intervention	*6 (35%)*	-
Blood transfusion given	*6 (35%)*	-
G-CSF given	*3 (18%)*	-

Discussion

This study found less favourable outcomes compared to the phase III PARAMOUNT study with a median PFS of 2.0 months in the current study compared to 4.4 months in the PARAMOUNT study [8]. Moreover, the PARAMOUNT study reported the mean number of cycles completed to be 7.9 compared to 5.9 in this study. A smaller phase II trial investigating the use of pemetrexed maintenance in NSCLC after a combination of carboplatin and pemetrexed induction treatment also found a favourable median PFS of 5.2 months when compared to the current study [12]. This study, therefore, suggests that pemetrexed may not be as efficacious as previously reported. However, the discrepancy in findings may be explained due to natural sampling variation in the current study as a result of a small sample size. Moreover, the PFS in this study was taken from the date of first maintenance pemetrexed dose and not the date of randomisation as in the PARAMOUNT study. Although the latter reports that the first cycle was administered within seven days of randomisation, this still represents a small source of lead time bias. In addition, the lack of a placebo control reduces the validity of the current study in its ability to suggest reduced efficacy for maintenance pemetrexed.

A further difference in study design was that patients with ECOG performance status 2 were also included in the current study whereas in the PARAMOUNT

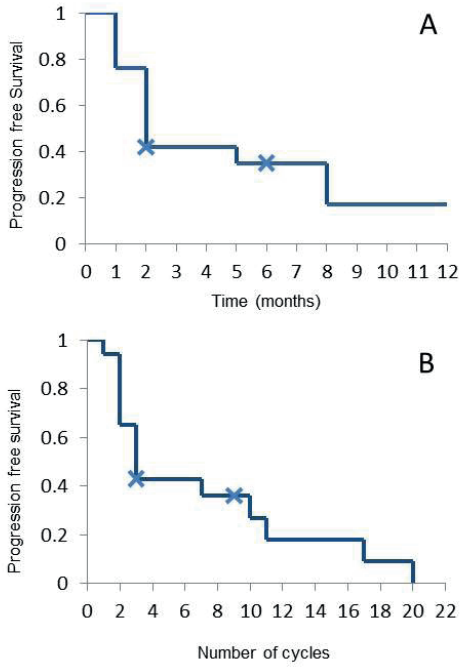

Figure 1: Kaplain-Meier survival analysis illustrating progression-free survival in months (a) and progression-free sutvival by numer of cycles (b). Blue crosses indicate censored data. Note that 2 patients were censored after 2 months (3 cycles) but only one blue cross is shown.

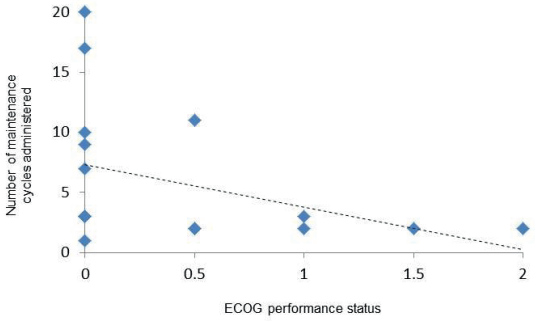

Figure 2: Scatter plot illustrating ECOG performance status against numer of pemetrexed maintenance cycles completed. A linear trend has been included (dashed line). Individual clinicians ranked patients as ECOG performance status 0/1 or 1/2 in cases where the categorisation was borderline; these are represented in decimal form.

study, only patients with ECOG performance status 0 and 1 were included. In the current study, 2 patients (12%) were classified as performance status > 1. As illustrated in figure 2, this study was able to demonstrate a statistically significant relationship between increasing ECOG performance status and decreasing number of pemetrexed cycles completed. This may partly explain the unfavourable PFS and total cycle numbers completed in this study. However, this is somewhat counterbalanced by the fact that there was a greater proportion of patients classified as ECOG performance status 0 in the current study when compared to those in the PARAMOUNT study (59% PS 0 in current study; 32% PS 0 in PARAMOUNT study).

Previous studies have suggested that patients with advanced NSCLC and poor ECOG performance status gain little benefit from maintenance gemcitabine [13, 14]. The current study provides evidence that increasing ECOG performance status also translates into reduced benefit from pemetrexed continuation maintenance in advanced NSCLC.

This study reported a higher rate of adverse events than in other studies [7, 12]. The total number of patients suffering at least one laboratory adverse event of any grade (82%, n = 14) and the number of patients with grade 3, 4 or 5 laboratory adverse events (12%, n = 2) was noticeably higher than in the PARAMOUNT study (any grade: 24%; G3, 4 or 5: 9%). This was also true for non-laboratory adverse events (current study: any grade 82%, G3, 4 or 5: 18%; PARAMOUNT: any grade 41%, G3, 4 or 5: 9%).

Interestingly, the final overall survival PARAMOUNT paper reported the rate of creatinine-based adverse events to be 2.5%, of which all were grade 1–2 [8]. The current study, using estimated glomerular filtration rate (eGFR) as a surrogate for renal function found that 47% of patients had grade 1–2 adverse eGFR events resulting in two patients being withdrawn from treatment. Furthermore, the current study found that 71% of all patients suffered a haemoglobin-based adverse event, with 35% of all patients receiving a blood transfusion. This was far greater than the rate of haemoglobin-based adverse events reported in the PARAMOUNT study (all grades: 14%) [7]. This suggests that the rate of adverse events for pemetrexed continuation maintenance chemotherapy may have been underestimated previously and that clinicians should closely monitor renal function and full blood count between each cycle.

This study has shown a higher than previously reported frequency of adverse events with maintenance pemetrexed and a predictable reduction in the efficacy of treatment with increasing ECOG performance status. As a result, clinicians should think carefully about initiating pemetrexed maintenance chemotherapy in any patient with even mildly limiting co-morbidity. All patients should have their renal function and full blood count vigilantly monitored between each cycle.

Acknowledgments

None

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin. 2011; 61: 69–90.
[2] Früh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical
[3] Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013; 24 (6): vi99–vi105.
[4] Li X, Wei S, Chen J. Critical appraisal of pemetrexed in the treatment of NSCLC and metastatic pulmonary nodules. Onco Targets Ther. 2014;7:937-45.
[5] Swisher SG. Surgical treatment of locally advanced non-small cell lung cancer. In: Fossella FV, Komaki R, Putnam JB Jr, eds. Lung Cancer. New York, NY: Springer, 2002: 118–41.
[6] Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2012; 23 (7): vii56–vii64.
[7] National Institute for Health and Clinical Excellence. Pemetrexed for the maintenance treatment of non-small-cell lung cancer. TA190. June 2010. Available at: http://www.nice.org.uk/guidance/TA190.
[8] Paz-Ares LG, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012; 13(3):247-55.
[9] Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013; 31(23):2895-902.
[10] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–16.
[11] Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 8/2006 update. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (accessed March, 2014).
[12] Oken, MM, Creech, RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.
[13] Minami S, Kijima T, Komuta K, et al. Phase II trial of pemetrexed continuation--maintenance after carboplatin-based induction in untreated non-squamous non-small cell lung cancer. Anticancer Res. 2013; 33(12):5535-42.
[14] Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase III trial. Lung Cancer. 2006; 52:155-163.
[15] Belani CP, Waterhouse DM, Ghazal H, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination therapy with gemcitabine carboplatin (G-Cb) for patients with advanced nonsmall cell lung cancer (NSCLC). J Clin Oncol. 2010; 28:540s.