

Impact of Pemetrexed Addition to Gemcitabine-Oxaliplatin on Treatment Outcome of Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer

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ABSTRACT

AIM Platinum-based doublets are the recommended standard first-line chemotherapy for stage IIIB/IV non-small-cell lung cancer (NSCLC). However, many studies have evaluated the benefit of using more intensive regimens that contain three cytotoxic agents. The aim of this study was to evaluate the benefits of adding pemetrexed to the combination of gemcitabine and oxaliplatin (GEMOX) in the management of non-squamous NSCLC.

METHODS Twenty eight evaluable patients with stage IIIB or IV non-squamous NSCLC were randomized to receive GEMOX doublet alone or GEMOX with pemetrexed (GEMOXAP). Dosages were gemcitabine 1250 mg/m² day 1, 8; oxaliplatin 100 mg/m² day 1 and pemetrexed 500 mg/m² day 1 with recycling every 21 days. Evaluation for response, toxicity and survival was performed after each circle.

RESULTS Partial response was higher but non-significant in the GEMOXAP arm (43.8%) compared to the GEMOX group (33.3%). Also higher but non-significant in the GEMOXAP group than the GEMOX group were the rates of improvement of dyspnea, hemoptysis, metastatic bone pain; quality of life; median time to disease progression and overall survival. Toxicity profiles were similar in the two groups.

CONCLUSION Large prospective studies are needed to establish whether the higher response rate, progression-free and overall survivals after addition of pemetrexed to the combination of gemcitabine and oxaliplatin are statistically significant in advanced non-squamous NSCLC.

Keywords: Pemetrexed; Oxaliplatin; Gemcitabine; Carcinoma, Non-Small-Cell Lung; Lung neoplasms.

INTRODUCTION

Unlike small cell lung cancer where chemotherapy is the modality of choice, the approach to non-small cell lung cancer (NSCLC) varies from surgical resection only to combined modalities depending on disease stage at presentation. NSCLC is the leading cause of cancer-related death. It comprises 80-85% of all cases of lung cancer. Pathological types include squamous, adenocarcinoma, large cell types in 35%, 30%, and 15% respectively. ¹ In a significant proportion of patients with metastatic or advanced disease, systemic chemotherapy treatment results in symptom control, maintenance of quality of life, and some prolongation of survival when compared with best supportive care alone. ^{2,3} Platinum-based doublets are the recommended standard first-line chemotherapy for stage IIIB/IV NSCLC and cisplatin is considered the mainstay of these combinations. ^{2,4} Oxaliplatin, a diaminocyclohexane third-generation platinum analogue, acts through DNA damage ⁵ and has less toxicity than and partial or no cross-resistance with cisplatin in a wide range of human tumors. ⁶ Gemcitabine (Gemzar) is a pyrimidine nucleoside antimetabolite. It is structurally related to 1-β-D-arabinofuranosyl-cytosine (ara-C). It inhibits cellular proliferation in S phase, and causes cells to accumulate in the G₁-S phase of the cell cycle. ⁷ Gemcitabine has been used for the treatment of patients with NSCLC. ^{8,9} Combinations of gemcitabine with platinum-based agents are among the most active chemotherapy regimens developed for advanced NSCLC. Many studies have evaluated the benefit of using more intensive regimens that contain three cytotoxic agents. Pemetrexed (Alimta) is a novel, multitargeted antifolate chemotherapy agent that is active in multiple tumor types including NSCLC. ^{10,11} Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate-binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms. Polyglutamated metabolites have a long intracellular half-life, resulting in prolonged drug action in malignant cells. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase

and glycinamide ribonucleotide formyl transferase, the latter of which is a folate-dependent enzyme involved in purine synthesis. ¹²

Pemetrexed has broad cytotoxic activity, as demonstrated by single agent and combination studies in lung cancer. ^{13,14} It attained regulatory approval as a single agent in previously treated advanced NSCLC on the basis of a phase III trial showing equivalent activity but diminished toxicity compared with docetaxel. ¹⁵ However, coadministration with gemcitabine had synergistic effect in vitro. ^{16,17} It was reported that the response rate to pemetrexed administered 90 min before gemcitabine was far superior to the response rate with the reverse sequence of administration. ¹⁸ Pemetrexed has variable effective responses on different pathological subtypes of lung cancer which is still under evaluation. This study set out to evaluate the benefits of adding pemetrexed to the combination of gemcitabine and oxaliplatin (GEMOX) in the management of non-squamous NSCLC.

PATIENTS AND METHODS

This was a comparative randomised study of twenty-eight patients from Saudi German Hospital in the Kingdom of Saudi Arabia covering the period from December 2006 to July 2009. The control group received gemcitabine 1250 mg/m² D1, 8 and oxaliplatin 100 mg/m² D1. This was repeated every 21 days. The study group received gemcitabine at a dose of 1250 mg/m² D1, 8; oxaliplatin 100 mg/m² D1 and pemetrexed 500 mg/m² intravenously (IV) day 1 with vitamin B12, folic acid, and dexamethasone. This was repeated every 21 days. All patients were to receive at least 3 cycles, except in case of progression, or unacceptable toxicity or patient refusal.

The cases were subjected to history taking, full clinical examination, laboratory and radiological investigations. Laboratory investigations included; complete blood picture, liver enzymes, alkaline phosphatase, serum creatinine and creatinine

clearance. All patients underwent chest X-ray & CT scan, abdominopelvic ultrasonography, bone scan and bronchoscope examination.

Inclusion criteria: 75 years \leq age \geq 18 years; ECOG performance status of 0-2; histopathological confirmation of non-squamous NSCLC by either CT-guided biopsy for peripheral lesions or bronchoscopic biopsy for central lesions; chemotherapy-naïve TNM stage IIIB or IV disease; measurable/evaluable lesions located outside irradiation fields; life expectancy of \geq 3 months; adequate hematopoietic reserve defined as absolute neutrophil count \geq 2000/mm³, platelet count \geq 100,000/mm³; and adequate hepatic and renal function defined as serum creatinine $<$ 1.5 times the upper limit of normal (ULN), creatinine clearance \geq 60 ml/min, serum bilirubin, AST and ALT $<$ 1.5 times ULN ($<$ 3 x ULN if hepatic metastases), alkaline phosphatase $<$ 3 times ULN, except in cases of bone metastases. All patients were required to provide signed informed consent.

Exclusion criteria included small cell or squamous types of lung cancer; prior chemotherapy treatment and evidence of grade \geq 1 peripheral neuropathy according to institutional and national guidelines; severe concomitant disease; and non-measurable disease.

The study was conducted in accordance with the Declaration of Helsinki on "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects."

DRUG ADMINISTRATION

Pemetrexed was given as a 10-minute intravenous infusion (IVI). Patients on the pemetrexed arm were instructed to take folic acid 350-1,000 μ g orally daily beginning approximately 1-2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. A 1,000 μ g vitamin B₁₂ injection was administered intramuscularly approximately 1-2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until after pemetrexed

discontinuation. Folic acid and vitamin B₁₂ were given because of their ability to reduce toxicities without affecting the efficacy of pemetrexed. Patients on the pemetrexed arm were further instructed to take dexamethasone (4 mg orally twice daily the day before, the day of, and the day after pemetrexed) as a prophylactic measure against skin rash. Gemcitabine was diluted with normal saline to obtain a final solution containing 10 mg/ml or less, and given as an intravenous infusion over 30 min, followed by oxaliplatin diluted in 500 ml of 5% glucose solution and administered as an IVI over 2 hrs, starting 15 min after the end of gemcitabine infusion. No specific hydration was given with oxaliplatin being devoid of nephrotoxicity. All patients received prophylactic anti-emetics, including at least one standard dose of a 5-hydroxytryptamine-3-receptor agonist, pre-medication consisted of 8 mg intravenous (IV) ondansetron combined with 80 mg IV methylprednisolone administered 30 min before the start of gemcitabine infusion.

PRETREATMENT AND FOLLOW UP EXAMINATION

Measurement of blood pressure was done on 2 consecutive days before, one week and 2 weeks after treatment. Tumor assessment was done by clinical examination, ultrasound, computed tomography (CT) scan and/or MRI as appropriate. Chest radiotherapy was done after six cycles of chemotherapy in patients with stage IIIB disease who responded. Radiation treatment was permitted after three cycles in patients who showed stable disease (SD) and at any time if disease progression (PD), if considered useful by treating physician. A minimum duration of four weeks was needed to document response. Response evaluation was performed every 3 cycles (every 2 months of treatment). Assessment was performed with the Response Evaluation Criteria in Solid Tumors (RECIST).¹⁹ The occurrence of an objective response had to be confirmed by a second evaluation 1 month after the first documentation. Physical examination, evaluation of drug-related toxicity according to the WHO Common Toxicity Criteria (CTC),²⁰ blood hematology and biochemistry were repeated on a weekly basis.

In this study, dose-limiting toxicity (DLT) was defined using the WHO CTC,²⁰ as any of the following events occurring during the first two cycles of treatment (first month of treatment): (i) grade 4 neutropenia lasting >7 days and/or associated with fever $\geq 38.5^{\circ}\text{C}$; (ii) grade 4 thrombocytopenia; (iii) grade 3 thrombocytopenia associated with hemorrhage; (iv) grade 3 non-hematological toxicity (excluding alopecia, nausea and vomiting); and (v) persistence of non-hematological toxicity (excluding alopecia) of CTC >2 at the scheduled retreatment. Oxaliplatin-induced neurotoxicity was graded according to an oxaliplatin-specific scale²¹ defined as follows—grade 1, hypoesthesia or paresthesia which completely resolved before the next cycle; grade 2, hypoesthesia or paresthesia which persist between cycles, without functional impairment; grade 3, permanent functional impairment. Grade 3 neuropathy was considered as a DLT. A delay of up to 2 weeks was permitted to allow the blood counts to return to \leq grade 1 toxicity level. On day 8, the full dose of gemcitabine was administered if ANC was $\geq 1,000/\mu\text{L}$ and PLT $\geq 75,000/\mu\text{L}$; the gemcitabine was not administered in case of grade 3/4 neutropenia or thrombocytopenia grade ≥ 2 . If febrile neutropenia occurred, then the dose of gemcitabine was reduced by 25% in subsequent cycles. Granulocyte-macrophage colony-stimulating factor (GM-CSF) would then be given in subsequent cycles. In case of a treatment delay ≥ 2 weeks or in case of permanent paresthesias, the oxaliplatin dose was reduced, but oxaliplatin was discontinued if there was grade 3 neurotoxicity as assessed according to the oxaliplatin-specific neurotoxicity scale. Supportive care that included blood-product transfusions, antibiotics, anti-emetics, analgesics and growth factors was given as appropriate. Palliative radiotherapy to previous painful lesions was allowed, as long as the patient did not have progressive disease and the irradiated lesion would not be the only measurable lesion.

STATISTICAL ANALYSIS

Primary end point was the rate of confirmed radiological tumor response in the intention-to-treat population. Differences in response rates between the two groups were evaluated by means of a two-

sided Fisher's exact test. P value of 0.05 or less was considered statistically significant. Secondary end points included time to progression, overall survival time, and incidence of adverse effects. The time to progression was calculated as the period from the date of randomisation to the first observation of disease progression or to death from any cause within 60 days after randomisation or the most recent tumor assessment. Overall survival time was calculated as period from date of randomisation until death from any cause or until the date of last follow-up, at which point data were censored. Statistical analysis was done using SPSS 10.0. The Kaplan–Meier method²² was used to estimate both time to progression and overall survival and these were compared using the log-rank test²³ between the study and control groups. Estimates of chemotherapy cycle costs were used to assess the cost-effective benefits in both treatment groups.

RESULTS

Of the 28 patients, 23 were male. The median age was 61 (36-75) years. Twelve control group cases received a median of 5 (3-8) cycles. Sixteen treatment group cases received a median of 6 (4-9) cycles. Stage IIIB and IV constituted (42.9%) and (57.1%) of total cases respectively (Table 1).

On bronchoscopy examination, central bronchogenic carcinoma was present in 17/28 cases (60.7%). Dyspnea was present either due to central obstructive lesions in 53.6% of total cases or peripheral lesion (pleural effusion) in 42.9% of cases. Haemoptysis was present in 35.7% of cases. Dysphagia and hoarseness were present in 3.6% and 7.1% of cases respectively. Cough and chest pain were present in 75% and 28.6% of cases respectively (Table 2). Metastatic lesions were present in (57.1%) of cases. Metastatic bone pain was present in 50% of cases, while jaundice and neurological manifestations were present in 17.9% and 10.7% of cases respectively (Table 2).

Hematological toxicity of grade 3/4 neutropenia and thrombocytopenia constituted 25% and 16.7%

Table 1: General characteristics of patients enrolled in the study

Criteria	Total No. (28 cases)	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)	P Value
Gender				
Male	23 (82.1%)	10 (83.3%)	13 (81.3%)	0.64
Female	5 (17.9%)	2 (16.7%)	3 (18.8%)	0.38
Stage				
III-B	12 (42.9%)	5 (41.7%)	7 (43.8%)	0.3
IV	16 (57.1%)	7 (58.3%)	9 (56.3%)	0.61
Elevated Biochemical marker				
SGOT	5 (17.9%)	1 (8.3%)	4 (25%)	0.22
Hypercalcemia	9 (32.1%)	3 (25%)	6 (37.5%)	0.26
Alkaline phosphatase	11 (39.3%)	5 (41.7%)	6 (37.5%)	0.3
Pathological Types				
Adenocarcinoma	18 (64.3%)	8 (66.7%)	10 (62.5%)	0.57
Large cell	10 (35.7%)	4 (33.3%)	6 (37.5%)	0.3

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed.

Table 2: Clinical picture of 28 evaluable cases of the study

Clinical symptoms	Total cases (28 cases)	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)	P Value
Central lung lesions				
Dyspnea	15 (53.6%)	8 (66.7%)	7 (43.8%)	0.21
Hemoptysis	10 (35.7%)	4 (33.3%)	6 (37.5%)	0.3
Dysphagia	1 (3.6%)	-	1 (6.3%)	0.57
Hoarseness	2 (7.1%)	-	2 (12.5%)	0.32
Peripheral lung lesions				
Cough	21 (75%)	9 (75%)	12 (75%)	0.67
Dyspnea	12 (42.9%)	6 (50%)	6 (37.5%)	0.24
Chest pain	8 (28.6%)	3 (25%)	5 (31.3%)	0.31
Central lung lesions				
Bony pains	14 (50%)	6 (50%)	8 (50%)	0.3
Jaundice	5 (17.9%)	3 (25%)	2 (12.5%)	0.36
Neurological	3 (10.7%)	2 (16.7%)	1 (6.3%)	0.39

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed.

respectively in the control group compared to 31.3% and 18.8% respectively in the treatment group as presented in Table 3. Partial response was present in 33.3% and 43.8% of cases in the control group and the treatment group respectively. Stable disease for more than 6 months was present in 41.7% of the control and 37.5% of the treatment group, Table 4.

Improvement of quality of life was higher in the treatment group. Dyspnea either due to central obstructive or peripheral restrictive lesions was improved in 45.3% of the control group compared to 29.2% of the treatment group. Improvement of hemoptysis occurred in 33.3% of cases in the control group and in 25% of cases in the treatment group, while improvement of metastatic bone pain occurred in 25% and 16.7% respectively (Table 5).

After median follow up duration of 15 (1.6-24) months it was found that median time to disease progression was 6.1 months (95% CI: 3.4- 8.8 months) and 7.1 months (95% CI: 2.7- 11.5 months) in the control and treatment groups respectively. Median survival was 15.6 (95% CI: 6.8-24 months) vs 11.3 (95% CI: 1.6-21 months) in the group of pemetrexed vs without pemetrexed respectively, (p=0.34). Median survival was 16.1 (95% CI: 8.1-24 months) vs 12.6 (95% CI: 4.7-21 months) for stage IIIB and 11.3 (95% CI: 6.8-14.9 months) vs 7.1 (95% CI: 1.6-12.2 months) months for stage IV in the group of pemetrexed vs without pemetrexed respectively. One-year survival was 62.5% vs 33.3% as presented in Table 6 and Figures 1 and 2.

Average cost of one chemotherapy cycle of gemcitabine and oxaliplatin combination was

about 6,880 Egyptian pounds (1,238 USD), as compared to the cycle of gemcitabine, oxaliplatin, and pemetrexed combination which cost average of 18,330 Egyptian pounds (3,299 USD) as shown in Table 7.

DISCUSSION

All patients were evaluable for response and toxicity. Patients' characteristics were well-balanced at baseline with no statistically significant differences between the two groups. Percentages of cases with cough and chest pain coincided with the findings of Martins SJ and Pereira JR.²⁴

Toxicities in both treatment arms were comparable without statistically significant difference. The duration of neutropenia and thrombocytopenia was usually less than 7 days. Recovery to normal at time of the subsequent planned infusion was experienced in the majority of cases. Febrile neutropenia that needed GM-CSF, isolation and antibiotics occurred in one patient in each arm. These were successfully treated with GM-CSF and broad-spectrum antibiotics. These toxicities were still tolerable and acceptable. There were no treatment-related deaths. Neurotoxicity was experienced in the first three treatment cycles. No patients had worsening of neurotoxicity after treatment discontinuation. The principal toxicities of pemetrexed were neutropenia, diarrhea, nausea/vomiting, mucositis, and skin rash.

Addition of pemetrexed to gemcitabine-oxaliplatin had higher response rate but with no statistical significance ($P=0.26$) which could be attributed to the relatively small sample size. Large prospective studies are needed to establish whether the higher response rate is statistically significant. Gemcitabine has response rates ranging from 20-30%. Gemcitabine combinations demonstrate comparable results to those of standard therapies in patients with extensive stages of lung cancer.²⁵ These results match previous studies which reported that third-generation platinum-based doublets represent the standard of care with response rates of 17% to 32% and 1-year survival rates of 30-45%.

^{26,27} Gemcitabine-platinum combinations result in additive and synergistic effects and yield response rates ranging from 38-54% in advanced NSCLCs with no overlapping toxicity.²⁸

Eberhardt W and Hepp R,²⁹ reported that combination chemotherapy with 2 drugs remains the standard of care in first-line treatment for patients with advanced and metastatic NSCLC, while three-drug regimens including newer drugs and platinum analogues showed some advantage in terms of time to progression vs 2-drug regimens, they may be significantly more toxic. However, addition of pemetrexed did not have more serious toxic effects.

This study showed that improvement of clinical symptoms either due to central or peripheral lung lesions or distant metastases was higher in the pemetrexed-oxaliplatin-gemcitabine arm at 16.7-50% compared to 12.5-33.3% in the oxaliplatin-gemcitabine arm with no statistical significance, which is consistent with the findings of Pectasides D and colleagues,³⁰ who reported that the clinical benefit of response which included improvement of performance status, dyspnea and anorexia, pain and cough reduction and cessation of hemoptysis and fever was observed in 10-50% of patients.

Median time to disease progression and survival were higher with addition of pemetrexed to oxaliplatin-gemcitabine than without pemetrexed. However, Scagliotti GV and colleagues¹³ reported lower rates than those found in this study. They reported median time to disease progression of 5.5 (95% CI: 1.6 – 11.2) months and median survival of 10.5 (95% CI: 6.6 – 24.3) months for patients who received pemetrexed-oxaliplatin.

For chemotherapy-naive patients with advanced NSCLC, addition of pemetrexed demonstrated an overall response rate of 15.8-23.3% and median survival times of 7.2 (95% CI: 3.6 – 11.2) and 9.2 (95% CI: 2.3 – 17.1) months.^{10,31} However in patients who had progressed during or within 3 months of completing first-line chemotherapy, the response rate was 8.9% with median survival time of 5.7 (95% CI: 1.1 – 9.2) months.¹⁰

Although it is difficult to compare efficacy results between phase II and phase III studies, it is notable that the objective response rates, median survival,

Table 3: Toxicity of treatment in both arms

Toxicity	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)	P Value
Hematological toxicity (grade III & IV)			
Anemia	1 (8.3%)	2 (12.5%)	0.44
neutropenia	3 (25%)	5 (31.3%)	0.31
Febrile neutropenia	1 (8.3%)	1 (6.3%)	0.51
thrombocytopenia	2 (16.7%)	3 (18.8%)	0.37
GIT toxicity (grade III & IV)			
Nausea/vomiting	3 (25%)	7 (43.8%)	0.19
diarrhea	1 (8.3%)	4 (25%)	0.22
mucositis	1 (8.3%)	6 (37.5%)	0.08
Neurotoxicity			
Grade II	3 (25%)	7 (43.8%)	0.19
Grade III	2 (16.7%)	4 (25%)	0.32
Fatigue	3 (25%)	7 (43.8%)	0.19
Skin rash	1 (8.3%)	4 (25%)	0.22
Alopecia	1 (8.3%)	2 (12.5%)	0.44
Elevated liver enzymes	2 (16.7%)	3 (18.8%)	0.38
Hypertension	1 (8.3%)	2 (12.5%)	0.44

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed

Table 4: Response of treatment in both treatment arms

Treatment outcome	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)	P Value
Partial response	4 (33.3%)	7 (43.8%)	0.26
Stationary disease	5 (41.7%)	6 (37.5%)	0.3
Disease progression	3 (25%)	3 (18.8%)	0.33

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed

Table 5: Subjective improvement of clinical symptoms in both treatment arms

Clinical symptoms	(Gem-Ox) No. (%)	(Gem-Ox-Pem) No. (%)	P Value
Central lung lesions			
Dyspnea	1/8 (12.5)	2/7 (28.6)	0.37
Hemoptysis	1/4 (25)	2/6 (33.3)	0.5
Dysphagia	-	-	1
Hoarseness	-	1/2 (50)	1
Peripheral lung lesions			
Cough	3/9 (33.3)	6/12 (50)	0.26
Dyspnea	1/6 (16.7)	1/6 (16.7)	0.55
Chest pain	1/3 (33.3)	1/5 (20)	0.54
Metastases			
Bony pains	1/6 (16.7)	2/8 (25)	0.46
Jaundice	-	1/2 (50)	1
Neurological	-	-	1

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed

and median time to progression for both regimens were comparable with the values reported in four large, randomized phase III studies evaluating platinum-based doublets (paclitaxel and cisplatin, gemcitabine and cisplatin, docetaxel and cisplatin, paclitaxel and carboplatin, vinorelbine and cisplatin,

and docetaxel and carboplatin).^{26,27} In these comprehensive clinical investigations, objective response rates range was 17-32%, median survival times ranged from 7.4-11.3 months and median time to progression ranged from 3.1-5.5 months.

Table 6: Survival and time to disease progression in both treatment arms

Treatment outcome	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)	P Value
Median time to progression (ms)	6.1 (3.4-8.8)	7.1 (2.7-11.5)	0.58
Median survival, all cases (ms)	11.3 (1.6-21)	15.6 (6.8-24)	0.34
Median survival (ms)			
Stage III-B	12.6 (4.7-21)	16.1 (8.1-24)	0.08
Stage IV	7.1 (1.6-12.2)	11.3 (6.8-14.9)	0.09
One year-survival	33.3%	62.5%	0.09

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed ; ms, months.

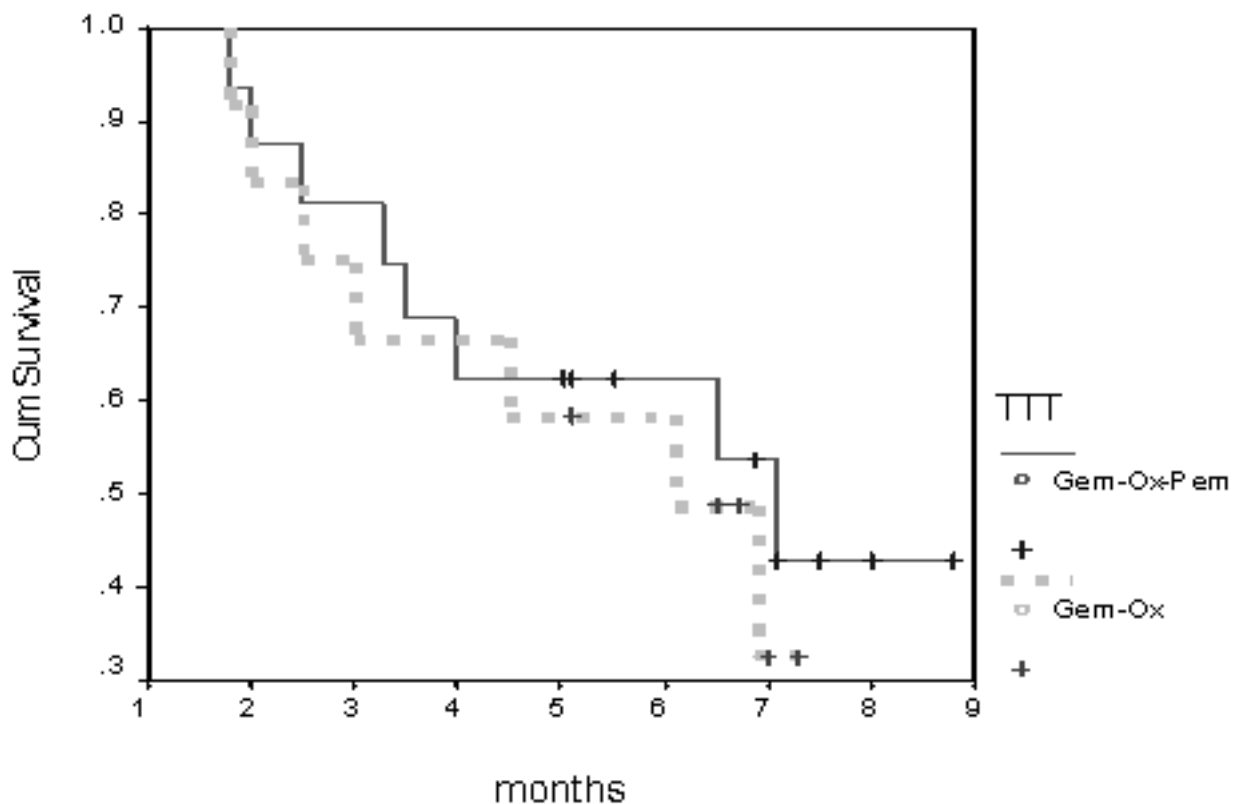


Figure 1. Progression-free survival in both treatment groups. Cum Survival, cumulative survival; Gem-Ox, Gemcitabine-Oxaliplatin; Gem-Ox-Pem, Gemcitabine-Oxaliplatin and Pemetrexed.

Scagliotti et al compared (pemetrexed-cisplatin) to (gemcitabine-cisplatin) as initial therapy in 1,725 patients with advanced NSCLC, and reported that survival was improved among patients with non-squamous NSCLC treated with pemetrexed-cisplatin compared with those treated with gemcitabine-cisplatin (11.8 months versus 10.4 months, respectively).³² However, survival was improved for patients with squamous cell type treated with gemcitabine-cisplatin (10.8 months) compared with those treated with pemetrexed-cisplatin (9.4 months). One potential explanation may relate to thymidylate synthase expression levels in NSCLC

histologic types. Overexpression of thymidylate synthase correlates with reduced sensitivity to pemetrexed.^{17,33} Baseline expression of thymidylate synthase gene and protein were significantly higher in squamous cell carcinoma compared with adenocarcinoma.³⁴ In addition, thymidylate synthase and S phase kinase-associated protein (Skp2) are transcriptionally regulated in the S phase of the cell cycle by transcription factor E2F-1.³⁵ Like thymidylate synthase, elevated expression of Skp2 has been more commonly found in patients with squamous cell lung carcinoma than adenocarcinoma.³⁶

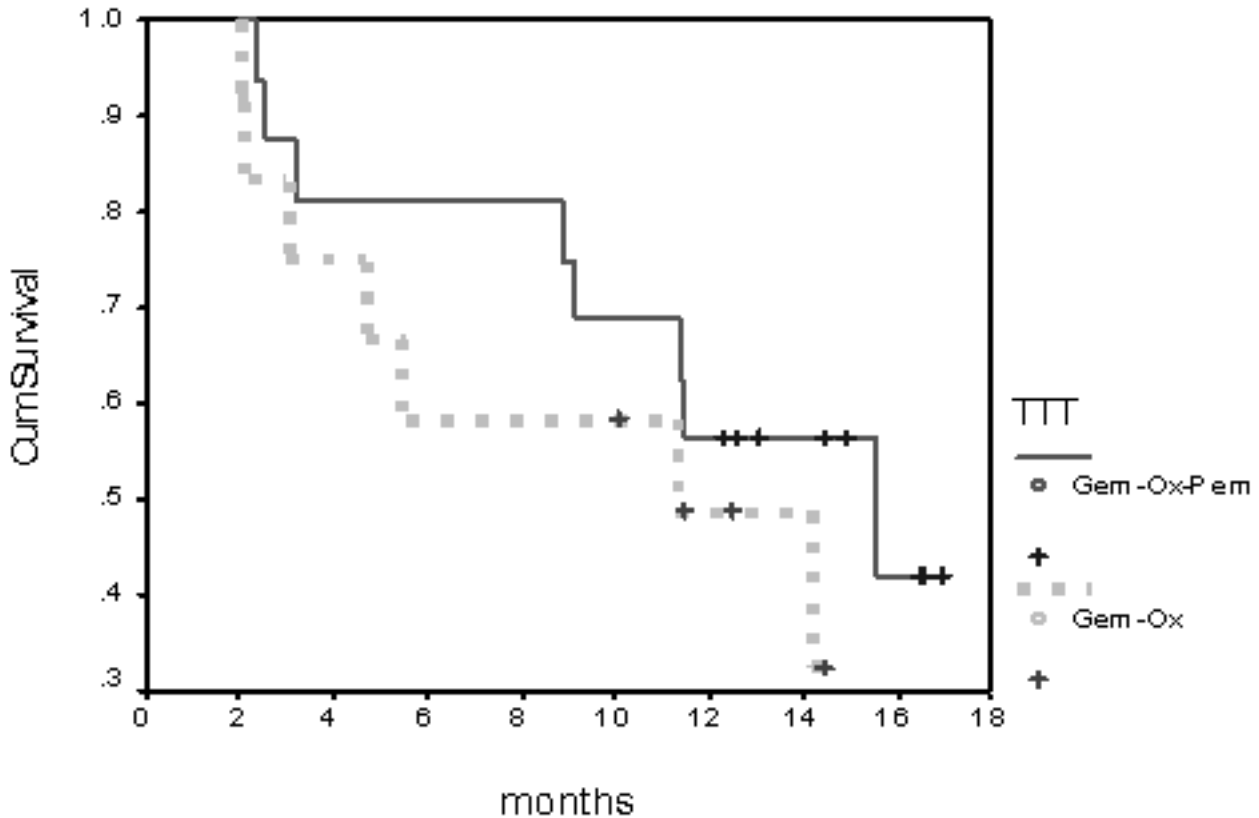


Figure 2. Overall survival in both treatment groups. Cum Survival, cumulative survival; Gem-Ox, Gemcitabine-Oxaliplatin; Gem-Ox-Pem, Gemcitabine-Oxaliplatin and Pemetrexed

Table 7. Cost of chemotherapy cycles in both groups of the study (by American dollars)

Cost	(Gem-Ox) (12 cases)	(Gem-Ox-Pem) (16 cases)
Cost of one cycle	1,238 ± 34	3,299 ± 27
Cost of 6 cycles	7,430 ± 41	19,796 ± 50

Gem, gemcitabine ; Ox, oxaliplatin; Pem, pemetrexed ; 1 Egyptian Pound = 0.18 American dollars.

Scagliotti et al also studied the predictive effect of histology for pemetrexed and found that nonsquamous lung cancer patients treated with pemetrexed-based therapy had statistically significant longer progression-free and overall survivals than their comparators.³⁷ Our findings are consistent with this data.

CONCLUSION

Pemetrexed seems to have higher response rate, progression-free and overall survivals in advanced/

metastatic lung cancer of adenocarcinoma and large cell pathological types. Large prospective studies are needed to establish whether this is statistically significant.

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FOOTNOTES

Contributors: All authors read and approved the final version of the manuscript.

Conflicts of interest: No conflict exists for drugs or devices used in the study.

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