RESEARCH ARTICLE

Gemcitabine Plus Paclitaxel as Second-line Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer

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Abstract

Purpose: The aim of this retrospective study was to determine response rates, progression-free survival (PFS), overall survival (OS) and toxicity of gemcitabine and paclitaxel combinations with advanced or metastatic non-small cell lung cancer patients (NSCLC) who have progressive disease after platinum-based first-line chemotherapy. Methods: We retrospectively evaluated the file records of patients treated with gemcitabine plus paclitaxel in advanced or metastatic NSCLC cases in a second-line setting. The chemotherapy schedule was as follows: gemcitabine 1500 mg/m^2 and paclitaxel 150 mg/m^2 administered every two weeks. Results: Forty-eight patients (45 male, 3 female) were evaluated; stage IIIB/IV 6/42; PS0, 8.3%, PS1, 72.9%, PS2, 18.8%; median age, 56 years old (range 38-76). Six (12.5%) patients showed a partial response (PR), 13 (27.1%) stable disease (SD), and 27 (56.3%) progressive disease (PD). The median OS was 6.63 months (95% CI 4.0-9.2); the median PFS was 2.7 months (95% CI 1.8-3.6). Grade 3 and 4 hematologic toxicities, including neutropenia (n=4, 8.4%), and anemia (n=3, 6.3%) were encountered, but no grade 3 or 4 thrombocytopenia. One patient developed febrile neutropenia. There were no interruption for reasons of toxicity and no exitus related to therapy. Conclusion: The combination of two-weekly gemcitabine plus paclitaxel was an effective and well-tolerated second-line chemotherapy regimen for advanced or metastatic NSCLC patients previously treated with platinum-containing chemotherapy. Although the most common and dose limiting toxicities were neutropenia and neuropathy, this regimen was tolerated well by the patients.

Keywords: Non-small cell lung cancer - second-line therapy - gemcitabine - paclitaxel

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Introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality and the incidence is increasing among women (Kosmidis et al., 2008). The American Cancer Society has estimated that the number of new lung cancer cases in the United States will be 114,690 in men and 100,330 in women for 2008. Among them, 161,840 are expected to die from this disease (Shepherd et al., 1993; Huang et al., 2008; Kosmidis et al., 2008; De et al., 2011). Most patients (>80%) have locally advanced stage III or metastatic stage IV NSCLC at the time of diagnosis and are ineligible for potentially curative surgery, and 5-year survival is <10% in this patient population (Shepherd et al., 1993; Walling et al., 1994; Caponi et al., 2010; De et al., 2011). Platinum-based chemotherapy offers a survival benefit in advanced NSCLC as compared with best supportive care and represents the standard of care. Non-platinum combinations can also provide modest survival benefits and improvements in quality of life, but these combinations have yet to be broadly accepted (Georgoulias et al., 2005; Treat et al., 2005; Takeda et al., 2009). During the past few years, several novel drugs including paclitaxel, docetaxel, pemetrexed, gemcitabine, vinorelbine, erlotinib, gefitinib have shown significant activity against NSCLC (Shepherd et al., 1993; Walling et al., 1994; Fosella et al., 2000; Shepherd et al., 2000; Smit et al., 2003; Delbaldo et al., 2004; Huang et al., 2008; Kosmidis et al., 2008; Di et al., 2010; Klastersky et al., 2012). As a single agent in advanced NSCLC, gemcitabine has produced response rates of between 20% and 28% and survivals between 7 and 11 months (Anderson et al., 1994; Shepherd et al., 2000). Platinum combination

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regimens with gemcitabine have resulted in response rates between 28% and 54% and 1-year survival rates between 35% and 61%, with manageable toxicity (Crino et al., 1997). Paclitaxel produces single-agent response rates between 20% and 42%, with 1-year survival rates of aproximately 40% in advanced NSCLC (Gatzemeier et al., 1995; Hainsworth et al., 1995; Bonomi et al., 2005; Paz-Ares et al., 2008). Gemcitabine and paclitaxel have shown independent activity in advanced NSCLC, lack overlapping toxic effects, and have different mechanisms of action. Preclinical studies indicate that in combination, gemcitabine–paclitaxel could have a synergistic effect (Grilli et al., 1993). Phase I and II trials of the combination have resulted in response rates between 27% and 47%, with manageable toxicity (Bhatia et al., 2002).

Only a few agents including docetaxel, pemetrexed, gefitinib and erlotinib have shown to be effective in the second-line and third-line chemotherapy for advanced NSCLC (Shepherd et al., 2005; Thatcher et al., 2005; Barlesi et al., 2006; Cullen et al., 2008; Kim et al., 2008; Scagliotti et al., 2009; Cappuzzo et al., 2010; Douillard et al., 2010; Reck et al., 2010; Vamvakas et al., 2010). Despite an increasing proportion of patients with advanced NSCLC derive prolonged survival with novel chemotherapy regimens; many of them will require salvage chemotherapy after relapse (Kosmas et al., 2007). Despite the improvement in treating advanced or metastatic NSCLC responses to modern platinum or non-platinum-based chemotherapy are still rarely results in long-term tumor control. For these reason development of effective second-line treatments is very important for advanced or metastatic NCSLC who have progressive disease after first-line treatment.

In this study we retrospectively evaluated response rates, progression-free survival (PFS), overall survival (OS) and toxicity of gemcitabine plus paclitaxel combination among patients with advanced or metastatic NSCLC patients who have progressive disease after the platinum-based first-line chemoterapy.

Materials and Methods

We retrospectively evaluated file records of 48 patients (45 male, 3 female) treated with gemcitabine plus paclitaxel in advanced or metastatic NSCLC who have progressive disease after the first-line chemoterapy in February 2008 from June 2010 in five centers in Turkey. Gemcitabine and paclitaxel schedule as follows: gemcitabine 1500 mg/m^2 infused >30 min and paclitaxel 150 mg/m^2 infused >3 h, both administered bi-weekly. Patients were pretreated with dexamethasone 16 mg i.v. before receiving paclitaxel. Patients were also premedicated with diphenhydramine 50 mg i.v. and a histamine H2-receptor antagonist before receiving paclitaxel. All of patients had recieved first-line chemoterapy (Table 1).

Toxic effects were graded according to World Health Organisation (WHO) criteria, and the worst score registered during treatment by each patient was recorded. Responses to treatment were evaluated after every four cycles by computed tomography of the chest, abdomen or the radiological examinations that detected the disease at other sites. Standard RECIST criteria were used for classifying tumor response. Complete response was as the disappearance of all known disease (target and non-target lesions). A partial response (PR) was defined as a 30% reduction from baseline in the sum of maximal diameters of the target lesions and a lack of disease progression in non-target lesions. Progressive disease (PD) was defined as the development of any new lesions or an increase of 20% in the maximal diameters of target lesions. Patients with stable disease (SD) did not meet the criteria for PR or PD. Duration of response was calculated from the date of initial therapy to the date of documented tumour progression, clinical deterioration, or death.

Statistical Analysis

Survival analyses were performed using Kaplan-Meier method. Progression-free survival (PFS) was defined as the time from diagnosis to disease relapse or death. Similarly, overall survival (OS) was calculated as the time

Table 1. Patients characteristics

		N
Number of patients		48
Sex	Male	45
	Female	3
Age (years)	Median	56
	Range	38-76
Performance status (ECOG scale)		
	0	4
	1	35
	2	9
Histology	Squamous carcinoma	19
	Adenocarcinoma	14
	Adenosquamous carcinoma	1
	Large cell carcinoma	2
	Bronchioaveolar carcinoma	1
	Undifferentiated carcinoma	1
Stage	IIIB	6
	IV	42
First-line chemoterapy regimens		
	Cisplatin with docetaxel	33
	Cisplatin with vinorelbine	6
	Carboplatin with vinorelbine	4
	Carboplatin with paclitaxel	2
	Cisplatin with etoposide	2
	Cisplatin with gemcitabine	1
Prior surgery		5
Prior radiotherapy	Chemo-radiotherapy	15
	Radiotherapy alone	4
	Cranial radiotherapy	7
	Bone radiotherapy	5
Metastasis sites	Bone	16
	Liver	9
	Brain	8
	Pleura	3
	Contralateral	13
	Nodes	8
	Surrenal	12
Number of metastasis sites	0	7
	1	21
	2	15
	3	4
	4	1

elapsed from the date of diagnosis to the date of death or the last visit. Statistical analyses were carried out using SPSS 15.0 program.

Results

Characteristics for these patients were summarized in Table 1. Median age was 56 (38-76) years old. The percentages of patients with smoking were 75% (median 25 pakcage/year), history of cancer in family were 18%, chronic obstructive lung disease were 8.2%. Five patients have had performed primary surgery, neoadjuvan chemothreapy delivered two patients who aplied surgery. Concurrent chemo-radiotherapy were aplied 15 patients (31.3%). The percentages of patients with palliative radiotherapy were (20.4%), 5 of them bone metastasis, 7 of them cranial metastasis. Most of the patients squamous cell cancer: squamous cell carcinoma 39.6%, adenocarcinoma 29.2%, 20.2% were not evaluated subtype of histologies. 8.3% of patients were in PS of 0, 72.9% in PS of 1, and 18.8% in PS of 2. Forty two patients (87.5%) were in stage IV, and metastatic site of disease was as follows: 16 patients (33.3%) had bone metastasis, 8 patients (16.7%) had brain metastasis, 12 patients (25%) had adrenal metastasis, 9 patients (18.8%) had liver metastasis, 13 patients (27.1%) had contralateral lung metastasis, 3 patients had pelural metastasis and 8 patients (16.7%) had lymph node metastasis. One patients had lenfanjitis carsinomatosa. The treatment was generally well-tolerated. Grade 3 and 4 hematologic toxicities including neutropenia (n=4, 8.4%), and anemia (n=3, 6.3%) were occurred (Table 2). There wasn't grade 3 or 4 thrombocytopenia. One patient developed febrile neutropenia. Dose reductions were required in 9 patients, 2 of them because of severe neutropenia and 7 of them grade 2 and 3 neuropathy. There were no interruption by reason of toxicity. Treatment-related death wasn't observed. Non-hematologic toxicities are summarized in Table 3. Median number of delivered cycles per patient was four (range 1-12). Six (12.5%) patients showed a partial response, 13 (27.1%) patients showed a stabil disease, 27 (56.3%) patients showed progressive disease. The median PFS was 2.7 months (95%CI 1.8-3.6) (Figure 1) and the median OS was 6.63 months (95%CI 4.0-9.2) (Figure 2).

Table 2. Hematologic toxicity

Toxicity	Number of patients N (%)			
	Grade 1	Grade 2	Grade 3	Grade4
Neutropenia	4 (8.3)	5 (10.4)	1 (2.0)	3 (6.25)
Trombocytopenia	3 (6.25)	1 (2.0)	0	0
Anemia	7 (14.6)	5 (10.4)	3 (6.25)	0

Table 3. Non-hematologic toxicities

Toxicity	Number of patients N (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis	1 (2.0)	1 (2.0)	-	-
Hepatotoxicity	3 (6.25)	-	-	-
Nephrotoxicity	4 (8.3)	-	-	-
Neurotoxicity	2 (4.2)	7 (14.6)	1 (2.0)	-
Diarrhea	2 (4.2)	2 (4.2)	-	-
Constipation	2 (4.2)	3 (6.25)	-	-
Nausea/ Emesis	8 (16.7)	4 (8.3)	1 (2.0)	-
Fatigue	5 (10.4)	6 (12.5)	-	-
Alopecia	5 (10.4)	1 (2.0)	-	-
Cardiac	-	-	-	-
Pulmonary	-	-	-	-
İnfection	-	1 (2.0)	-	1 (2.0)

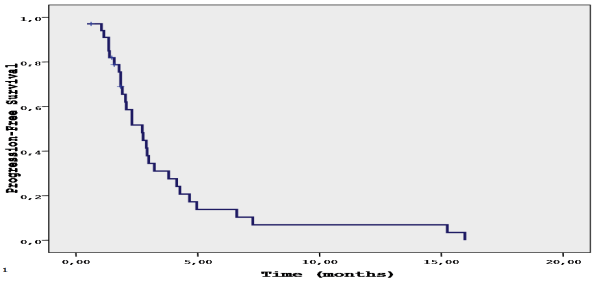

Figure 1. Progression-Free Survival.

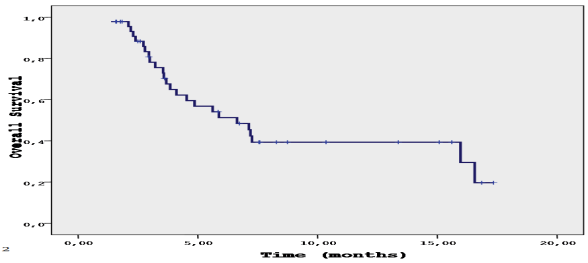

Figure 2. Overall Survival.

Discussion

In the recently several studies investigated the role of second-line therapies in advanced NSCLC. Based on these trials, docetaxel or pemetrexed suggested the main chemotherapeutic options, and erlotinib is the biological alternative to chemotherapy, mainly in non-smoker females with adenocarcinoma (Hana et al., 2004; Barlesi et al., 2006; Cullen et al., 2006; De et al., 2008; Gridelli et al., 2008; Stinchombe et al., 2008; Scagliotti et al., 2009).

Many other trials comparing a combined chemotherapy versus single-agent chemotherapy as second-line treatment in NCSLC. These trials showed that combined chemotherapy significantly increases response rate and progression-free survival, but is more toxic and does not improve overall survival compared to single-agent chemotherapy (Georgoulias et al., 2004; Georgoulias et al., 2005; Pectasides et al., 2005; Wachters et al., 2005; Smit et al., 2008; Di et al., 2009; Gebbia et al., 2009; Takeda et al., 2009; Tucker, 2010)

A number of studies single-agent chemotherapy with gemcitabine as second-line treatment in advanced NSCLC have been showed that median OS, 22 weeks to 8.3 months, RR 3-25% (Androulakis et al., 1998; Crino et al., 1999; Gridelli et al., 1999). Coskun et al. study, 21 patients treated with single agent gemcitabine as a second-line treatment and reported a partial response rate 19%, stabil disease rate 29%, median OS was 36 weeks. Only one patients experienced grade ¾ hemathologic toxicity in this study (Coskun et al., 2008).

Single-agent chemotherapy with paclitaxel as second-line treatment in advanced NSCLC have been showed

that median OS 17 weeks to 10 months, RR 0-38% (Hainsworth et al., 1995; Androulakis et al., 1998; Socinski et al., 1999; Bonomi et al., 2005; Coskun et al., 2008; Paz-Ares et al., 2008).

Gemcitabin and paclitaxel have been studied Phase II/III trials in patients with no prior chemotherapy recieved advanced NSCLC. These trials showed that median OS, 6.7-13.3 months, median PFS 3.5-8.3 monts, RR 32-35%, 1 year survival rate 26.7-41.1 with this treatment. Grade 3 and 4 hemathologic toxicities were seen; neutropenia 6-22%, trombocytopenia 1-7%, anemia 1.6-6%. Grade 3/4 non-hemathologic toxicities were seen; neurotoxicity 3.5-6.8%, nephrotoxicity 0-0.5%,, hepatotoxiciy 0-7%, pulmoner toxicity 0-13.8 (Isla et al., 2001; Smit et al., 2003; Kosmidis et al., 2008; Pino et al., 2008; Comellaa et al., 2010).

Mori et al.'s study, patients treated with paclitaxel and gemcitabine as second-line treatment for advanced NSCLC after treatment with platinum-based chemotherapy. Partial response rate was 37.5%, SD rate was 65%, PD rate was 12.5%. The median OS was 41.7 weeks, the median PFS was 19 weeks, grade $^3/_4$ hematologic toxicities included neutropenia (60%), anemia (15%), and thrombocytopenia (12.5%) were observed (Mori et al., 2007). In our study partial response rate was 12.5%, SD rate was 27%, PD was 56.3%, median PFS was 2.7 months (95%CI 1.8-3.6) and median OS was 6.63 months (95%CI 4.0-9.2). Grade $^3/_4$ hematologic events, including neutropenia (8.4%), and anemia (6.3%) were occurred. There wasn't grade $^3/_4$ thrombocytopenia. These consequencies were shorter and worse than Mori et al.'s study. When we looked at patients characterictics in our study a greater number of patients had stage 4 disease and had liver metastasis unlike the study of Mori et al. and we observed significantly less hemathologic toxicities than Mori's study.

Androulakis et al. (1998) gemcitabine and paclitaxel were administered as a second-line setting patients with NSCLC and reported that the median survival was 11 months, the median TTP 8 months; CR rate was 2% (1/49); PR rate was 16% (8/4); SD rate was 29% (14/49), PD rate was 53% (26/49). The toxicity profile was grade 3/4 neutropenia and thrombocytopenia occurring in 12% and 2% respectively (Androulakis et al., 1998). In our study we detected median PFS and median OS was shorter than this study; and we found similar PR, SD and PD rates. We thought that these results due to poor performance status of our patients and also high incidence of liver and brain metastasis in our patients. Grade 3/4 hematologic and nonhemathologic toxicities were aproximately similar.

In conclusion, the combination of gemcitabine and paclitaxel is an effective and well-tolerated second-line chemotherapy regimen for advanced or metastatic NSCLC patients who previously treated with platinum-containing chemotherapy. The most common and dose limiting toxicities were neutropenia and neuropathy and an unexpected toxicity wasn't observed. In our study two-weekly gemcitabine plus paclitaxel therapy was tolareted well by the patients whose performance status was relatively worse. The treatment schema which causes the least toxicity and effects the performance status minimally is not well known; but the two-weekly schema may be suitable relevant for these patients. Conflict of interest disclousores: All authors have agreed there is no conflict of interest.

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