RESEARCH ARTICLE

Comparison of Single Agent Gemcitabine and Docetaxel in Second-Line Therapy for Advanced Stage Non-Small Cell Lung Cancer in a University Hospital in Turkey

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Abstract

Purpose: To compare the efficacy and toxicity of gemcitabine versus docetaxel in a second-line setting of nonsmall cell lung cancer (NSCLC) patients previously treated with platin-based combination chemotherapy. Materials and Methods: We retrospectively evaluated the medical records of 57 patients treated with single agent gemcitabine or docetaxel in second-line setting of advanced NSCLC who received one prior platinum-based therapy. Results: The mean age was 56.7±8.39 years with 55 (96.5%) males and two (3.5%) females. Forty of them received docetaxel and 17 gemcitabine. The mean number of chemotherapy cycles was 6.8±4.0 in the gemcitabine group, while it was 4.6±3.0 in the docetaxel group. Overall response rates were 8% and 12% (P=0.02) for gemcitabine and docetaxel, respectively. The median survival time was 22 versus 21 months for gemcitabine and docetaxel, respectively. The median times to progression were 8 and 5 months. There was no difference between the two groups in terms of incidence of adverse affects (40% *vs* 47.1%). All of the hematological side effects were grade 1/2. No major toxicity was encountered necessitating stopping the drug for either group. Conclusions: Treatment with gemcitabine demonstrated clinically equivalent efficacy with a significantly improved safety profile compared with those receiving docetaxel in the second-line setting for advanced NSCLC in this study. Based on these results, treatment with gemcitabine should be considered a standard treatment option for second-line NSCLC.

Keywords: Gemcitabine and docetaxel - second-line therapy - advanced stage non-small cell lung cancer

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Introduction

Lung cancer is one of the most common causes of death among malignant tumors (Cobo et al., 2007). Despite an increasing proportion of patients with advanced non-small cell lung cancer (NSCLC) derive prolonged survival with novel chemotherapy regimens; many of them will require second-line chemotherapy after relapse (Kosmas et al., 2007). Several agents including docetaxel, gemcitabine, pemetrexed and erlotinib have shown to be effective in the second-line chemotherapy for advanced NSCLC (Hertel et al., 1990, Lund et al., 1993, Fossella et al., 2000, Shepherd et al., 2000, Juergens et al., 2007).

Gemcitabine (20, 20-difluorodeoxycytidine) is a nucleoside analog that possesses a unique mechanism of action that provides a much wider range of antitumor activity (Hertel et al., 1990, Lund et al., 1993). There was no randomized study comparing single agent gemcitabine with other agents known to be effective in the second-line setting.

Docetaxel, which is a semisynthetic taxane analogue with definite activity in patients with NSCLC and its value as a single agent has been determined in patients with NSCLC with exposure to prior treatment. Docetaxel monotherapy, at a dose of 100 mg/m^2 administered once every 3 weeks, has shown promising activity as a second-line treatment for NSCLC (Fossella et al., 2000, Shepherd et al., 2000).

In this study, we evaluated the affectivity and toxicity profiles of single agent gemcitabine and docetaxel in the second-line setting of advanced NSCLC patients previously treated with a combined platinum-based therapy

Materials and Methods

We retrospectively evaluated the medical records of 57 patients treated with single agent gemcitabine or docetaxel in second-line setting of advanced NSCLC. The inclusions criteria were as follows: Patients with histologically confirmed advanced NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, progression during or after the completion of one prior platin-based combined chemotherapy, no history of other malignancies and age 18-75 years. Patients with brain metastases were eligible if they had been irradiated,

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the brain lesions were radiologically stable and clinical improvement was evident.

Treatment consisted of IV gemcitabine 1.250 mg/m^2 on days 1 and 8, followed by a 1-week rest repeated every 3 weeks and IV docetaxel 75 mg/m^2 in a 3-week schedule.

Doses were reduced by 50% if patients experienced leukopenia (WBC\1.500/dl) and thrombocytopenia (platelet\100.000/dl). Chemotherapy was omitted if WBC count less than 1.000/dl and platelet less than 50.000/dl. Treatment was stopped if disease progression or major toxicities occured or according to physician's decision.

Evaluation of response was performed every two cycles of therapy with computed tomography scans of the chest. Responders were defined as complete response (CR, disappearance of assessable disease) or partial response (PR, reduction of more than 50% of the lesion of the two largest tumor diameter). Stable disease (SD) meant less than 25% increases in tumor size. Progressive disease (PD) was defined by an increase of more than 25% in tumor size.

The overall survival (OS) time was calculated as the period from the start of chemotherapy until death from any cause or until the date of the last follow-up. Overall survival times were estimated by the Kaplan-Meier method. Survival curves were compared with the log-rank test. P values less than 0.05 were accepted as significant.

Results

Fifty-seven patients were included in this study, forty of them received docetaxel and seventeen of them received gemcitabine as a second-line therapy. There was no significant difference between the two groups with regard to gender, age, performance status, disease stage, tumor histology and smoking habit. Most of the patients (94.1%) in the gemcitabine group had received the cisplatin/docetaxel combination therapy in the first-line setting. Majority of the patients (55.0%) in the docetaxel group had received cisplatin/vinorelbine combination (Table 1). Fifty-one patients received at least two cycles of second-line therapy and were evaluable for response, and all patients were evaluable for toxicity.

In the dosetaxel group, the median patient age was 56 years (range, 41-75 years), and the median performance status (ECOG) was 0 (range, 0-2). With regard to gender, 38 patients were male, and 2 patients were female. There were 15 patients with Stage III disease, and 25 patients

Table 1. Table: Characteristics of the Groups

Characteristics	Docetaxel N (%)	Gemcitabine N (%)	Total N (%)	p
Total patients	40 (70.2)	17 (29.8)	57 (100)	
Gender			0.348	
Male	38 (95)	17 (100)	55 (96.5)	
Female	2 (5)	0 (0)	2 (3.5)	
Age (yrs)				0.859
Mean±standard deviation	56.8±8.8	56.4±7.5	56.6±8.1	
Range	41-75	45-74	41-75	
Smoking history				0.227
Nonsmoker	3 (7.5)	0 (0)	3 (5.3)	
Ex-smoker	7 (17.5)	1 (5.9)	46 (80.7)	
Current smoker	30 (75.0)	16 (94.1)	8 (14)	
Performance status (ECOG)				0.292
0	27 (67.5)	10 (58.8)	37 (64.9)	
1	10 (25)	7 (41.2)	17 (29.8)	
2	3 (7.5)	0 (0)	3 (5.3)	
Stage at initial diagnosis				0.357
IIIA	4 (10.0)	4 (23.5)	8 (14.0)	
IIIB	11 (27.5)	5 (29.4)	16 (28.1)	
IV	25 (62.5)	8 (47.1)	33 (57.9)	
Histology				0.356
Squamous cell carcinoma	21 (52.5)	11 (64.7)	33 (57.8)	
Adenocarcinoma	11 (27.5)	2 (11.8)	13 (22.8)	
Adenosquamous	0 (0)	1 (5.8)	1 (1.8)	
Unspecified	8 (17.5)	3 (17.6)	11 (19.2)	
Previous first-line chemotherapy				0.001
Carboplatin/Paclitaxel	4 (10.0)	1 (5.9)	5 (5.8)	
Carboplatin/Gemcitabine	5 (12.5)	0 (0)	5 (8.8)	
Carboplatin/Vinorelbine	1 (2.5)	0 (0)	1 (1.8)	
Cisplatin/Gemcitabine	6 (15.0)	0 (0)	6 (10.5)	
Cisplatin/Docetaxel	2 (5.0)	16 (94.1)	18 (31.6)	
Cisplatin/Vinorelbine	22 (55.0)	0 (0)	22 (38.6)	
Metastasis Site				0.102
Brain	7 (17.5)	5 (29.4)	12 (21.1)	
Bone	8 (20)	1 (5.8)	9 (15.8)	
Surrenal	1 (2.5)	0 (0)	1 (1.7)	
Other	1 (2.5)	1 (5.8)	2 (3.5)	

*ECOG: Eastern Cooperative Oncology Group (ECOG)

Table 2. Treatment Responses and Survival of Patients

Variables	Dosetaxel n (%)	Gemcitabine n (%)	Total n (%)	p
Response rates (%)				>0.05
Complete response	0 (0)	1 (5.8)	1 (1.7)	
Partial response	3 (7.5)	2 (11.7)	5 (8.7)	
Stable disease	9 (22.5)	5 (29.4)	14 (24.5)	
Progressive disease	28 (70.0)	9 (52.9)	37 (64.9)	
Overall response rate (%)	12	8	20	0.02
Chemotherapy cycles-mean	4.6±3.0	6.8±4.0	5.4±3.2	0.07
PFS*	6.5±5.5	9.9±7.6	7.6±6.1	0.06
Overall survival (months)	21.1±11.4	24.6±12.4	22.2±11.7	0.313

*PFS=Progression-Free Survival

Table 3 Toxic Effects of the Group

Type of Toxicity	Dosetaxel n(%)	Gemcitabine n(%)	Total n(%)	p
None	24(60)	9(52.9)	33(57.9)	0.621
Yes	16(40)	8(47.1)	24(42.1)	0.303
Anemia	1(2.5)	0	1(1.7)	
Nausea and vomiting	2(5)	0	2(3.5)	
Weakness and Anorexia	0	1(5.8)	1(1.7)	
Hypercalcemia	1(2.5)	0	1(1.7)	
Liver toxicity	0	1(5.8)	1(1.7)	
Renal toxicity	0	2(11.7)	2(3.5)	
Neutropenia	2(5.0)	0	2(3.5)	
Pneumonia	4(10.0)	4(23.5)	8(14)	
Lung toxicity	1(2.5)	0	1(1.7)	
Thrombophlebitis	1(2.5)	0	1(1.7)	

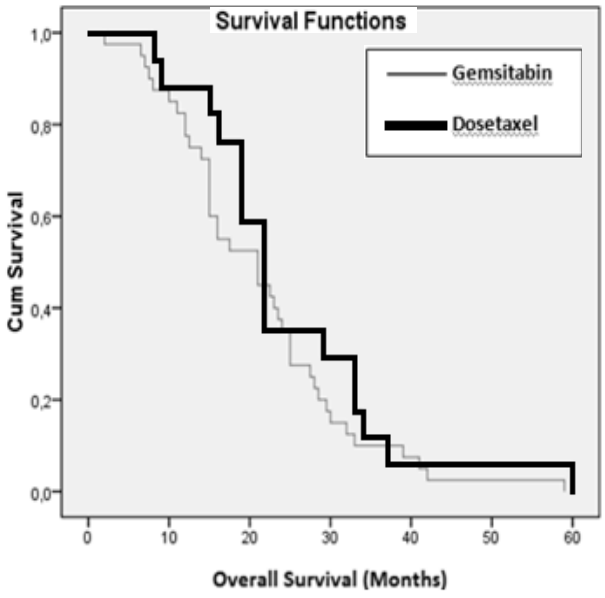

Figure 1. Survival Curves

with Stage IV disease at the time of initial diagnosis. Tumor histology included 11 patients with adenocarcinoma, 21 patients with squamous cell carcinoma, and seven patients with tumors of unspecified histology. Four of them had received paclitaxel/carboplatin, 5 of them gemcitabine/carboplatin, one patient vinorelbine/carboplatin, 6 of them gemcitabine/cisplatin, 2 of them docetaxel/cisplatin, 22 of them vinorelbine/cisplatin as firstline chemotherapy.

In the gemcitabine group, the median patient age was 56.4 years (range, 45-74 years), and the median performance status (ECOG) was 0 (range, 0-2). With regard to gender, all of the 17 patients were male. There were 9 patients with Stage III disease, and 8 patients with Stage IV disease at the time of initial diagnosis. Tumor histology included 2 patients with adenocarcinoma, 11 patients with squamous cell carcinoma, 1 patient with adenosquamous carcinoma and three patients with tumors of unspecified histology. Only one patient had received paclitaxel/carboplatin and the rest of the patients had received docetaxel/cisplatin as a first line chemotherapy.

Six patients (10.6%) were resistant to first-line treatment (experienced progressive disease (PD) or recurrent disease within 3 months from completion of first-line treatment), whereas the remaining 51 patients (89.4%) were sensitive to platinum-based therapy and experienced disease recurrence after a prior response that lasted 3 months from the end of first-line chemotherapy. Three (7.5%) patients showed a partial response (PR), 9 (22.5%) stable disease (SD), and 28 (70%) PD in the docetaxel group. One (5.8%) complete response was observed in gemcitabine group. Two (11.7%) patients showed PR, 5 (29.4%) SD, and 9 (52.9%) PD. The overall response rate was 12% within the docetaxel group. In the gemcitabine group, the overall response rate was 8%, this difference was statistically significant (p=0.02). The mean number of chemotherapy cycles was 6.8±4.0 in the gemcitabine group, on the other hand it was 4.6±3.0 in the docetaxel group.

The median OS was 21 months; the median PFS was 5 months in the gemcitabine group and the median OS was 22 months, the median PFS was 8 months in the docetaxel group. Altough PFS was longer in the gemcitabine group, it was not statistically significant (p=0.06) (Figure 1).

Toxic effects are shown in Table 3. All side effects were grade 1/2. There was no difference between the two groups in terms of incidence of the adverse affects (40% vs 47.1% p=0.303). Hematological toxicity was reported by 3 (7.5%) patients in the docetaxel group. No hematological side effect was seen in the gemcitabine group. None of the patients experienced grade 3/4 neutropenia. No major toxicity was encountered to stop the drug for both groups. Patients receiving gemcitabine were more likely to have nonhematological side effects. One patient had weakness and anorexia, liver enzymes was elevated in one patient, two patients had renal toxicity and 4 patients developed pneumonia.

Discussion

Platinum-based chemotherapy was the standard

first-line treatment for locally advanced or metastatic NSCLC. However, nearly all patients exposed to first-line chemotherapy eventually experience progression. At present, docetaxel was the commonly used second-line chemotherapy for advanced NSCLC, but the benefit was modest. There are only few agents approved for second-line chemotherapy of advanced NSCLC including docetaxel, pemetrexed and erlotinib (Juergens et al., 2007; Fossella et al., 2000, Shepherd et al., 2000). In this study, we evaluated the affectivity and toxicity profiles of single agent gemcitabine and docetaxel in the second-line treatment and according to our knowledge, this is the first report to compare second-line gemsitabine with docetaxel for advanced NSCLC patients from Turkey.

Docetaxel has been extensively evaluated in the second-line setting. Seven Phase II trials of this agent have been reported, enrolling a total of 312 patients who were treated with docetaxel 100 mg/m^2 every 3 weeks. Overall response rates (OR) ranged from 14-24%, and the median survival time was between 6 and 11 months in these studies (Burris et al., 1993, Yokoyama et al., 1994, Chevalier et al., 1995, Fossella et al., 1995, Mattson et al., 1996, Robinet et al., 1996, Gandara et al., 1997, Robinet et al., 1997). In our study OR of dosetaxel was found 12% and the 21 months median survival in our study is similar to the median survival achieved in previous studies.

In one study, overall response rates of 11.9% and 7.5% were obtained for docetaxel at doses of 100 mg/m^2 and 75 mg/m^2, respectively (Fossella et al., 2000). In our study, overall response rate was 12%.

The side-effects reported from the previous studies with docetaxel including diarrhoea, neuropathy, and grade 3 and 4 neutropenia were not seen in our patients. The most common side affects were pneumonia and grade 1/2 neutropenia with the rate of 10.0% and 5% respectively. One of the reasons for the less side effects may be the higher performance scores (92.5%) of our patients. Before and after the each cycle of chemotherapy, complete blood count and biochemistry values of the all patients closely followed. Chemotherapy was received if WBC count above 1.000/dl and platelet above 50.000/dl. Close monitarization may be the another reason for the apperance of the less side affects.

Phase II trials, evaluating activity and tolerability of single agent gemcitabine as second line chemotherapy, demonstrated response rates ranging from 6% to 20.6% (Crino et al., 1999, Gridelli et al., 1999, Van Kooten et al., 1999, Gillenwater et al., 2000, Sculier et al., 2000, van Putten et al., 2001, Lara et al., 2004).

Cho et al. tested gemcitabine as single agent in 83 platinum pretreated patients with advanced NSCLC. In this study, patients received gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days. Sixteen patients (19%) achieved a partial response (PR) to treatment; the median duration of response was 29 weeks (Cho et al., 2006). In our study, patients received gemcitabine 1.250 mg/m^2 on days 1 and 8, followed by a 1-week rest repeated every 3 weeks. One (5.8%) complete response was observed, two (11.7%) patients showed a PR.

In another study, Gridelli et al. evaluated a 4-week schedule of single agent gemcitabine in 30 platinum-pretreated advanced NSCLC patients. Six (20%) partial responses were observed, two of which in patients progressing during first line chemotherapy (Gridelli et al., 1999).

Crino et al. and Cho et al. reported 34 and 38 weeks of median overall survival respectively (Crino et al., 1999, Cho et al., 2006). In our study, the median survival of patients who received gemcitabine was 22 months. Median time to disease progression was 8 months. Gemcitabine was well tolerated in our patient population. Among all of the chemotherapy cycles, we had not observed any grade 3 and 4 toxicities.

In previous studies, overall response rate was between 18.5% and 19% in the treatment of single agent gemcitabine as a second treatment (Cho et al., 2006, Coskun et al., 2008). Overall response rate was higher in the group receiving docetaxel (12% vs 8%) and PFS and OS were longer in the gemcitabine group (but not istatistically sagnificant).

We concluded that docetaxel and gemsitabine are statistically equivalent in terms of OS and toxicity. Treatment with gemcitabine demonstrated clinically equivalent efficacy with a significantly improved safety profile compared with those receiving docetaxel in the second-line setting for advanced NSCLC in this study. Based on these results, treatment with gemcitabine should be considered a standard treatment option for second-line NSCLC.

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