Effectiveness of gemcitabine as second-line chemotherapy in non-small cell lung cancer

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ÖZET

Küçük hücreli dışı akciğer kanserinde ikinci basamak kemoterapi olarak gemsitabinin etkinliği

Küçük hücreli dışı akciğer kanseri (KHDAK)'nde platin bazlı kemoterapiden sonra kullanılan ikinci basamak kemoterapiyle ilgili belirsizlikler devam etmektedir.

Bu retrospektif çalışmada daha önce kemoterapi alan ve yanıt alınamayan veya daha sonra nükseden KHDAK'lı 34 hastada ikinci basamak kemoterapi için kullanılan tek ajan gemsitabinin etkisi değerlendirilmiştir. Gemsitabin, üç haftada bir, birinci ve sekizinci günlerde ve 1250 mg/m^2 dozunda intravenöz olarak kullanılmıştır.

Median yaşın 50 olduğu ve en çok skuamöz hücreli karsinom (%44.1) tipinin görüldüğü belirlenmiştir. Yanıt oranları değerlendirildiğinde tam yanıtın hiçbir hastada olmadığı, yedi hastada (%20.6) kısmi yanıtın elde edildiği ve median sağkalımın 29 hafta olduğu saptanmıştır. Bir yıllık sağkalım olasılığının %26.5, progresyona kadar geçen median sürenin ise 13 hafta olduğu belirlenmiştir. Uygulanan toplam 119 kemoterapi siklusu içerisinde grade III ve IV toksisitenin siklusların sadece %2.5'inde ortaya çıktığı ve bu hasta grubunda gemsitabinin iyi tolere edildiği görülmüştür.

Çalışmanın tüm sonuçları değerlendirildiğinde KHDAK'nin ikinci basamak kemoterapisinde tek ajan olarak gemsitabinin orta derecede etkili olduğu, iyi tolere edildiği ve tedavi seçenekleri arasında düşünülebileceği sonucuna varılmıştır.

Anahtar Kelimeler: *Gemsitabin, küçük hücreli dışı akciğer kanseri, ikinci basamak kemoterapi.*

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SUMMARY

Effectiveness of gemcitabine as second-line chemotherapy in non-small cell lung cancer

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The role of a second-line chemotherapy after an initial treatment with a platinum-based regimen remains largely undefined. In this retrospective clinical effectiveness study, gemcitabine as monotherapy was evaluated in the second-line chemotherapy in 34 non-small cell lung cancer (NSCLC) cases that had been previously received chemotherapy and did not respond to the treatment or presented with relapses. Gemcitabine was given intravenous at a dose of 1250 mg/m^2 on days one, eight every three weeks. Median age was 50 years and squamous cell carcinoma was the most common malignancy (44.1%). No patient had a complete response, 7 (20.6%) patients had a partial response. The median survival was 29 weeks. The 1-year survival probability was estimated at 26.5%. Median time to disease progression was 13 weeks. Gemcitabine was well tolerated in this patient population. Among totally 119 chemotherapy cycles, we observed grade 3 and 4 toxicities only in 2.5% of cycles. As a result of the study, single agent gemcitabine is found to be tolerable and to have moderate effectiveness in the second-line chemotherapy in NSCLC. It should be placed among treatment options.

Key Words: *Gemcitabine, non-small cell lung cancer, second-line chemotherapy.*

At the beginning of twentieth century, lung cancer was a rare disease. However, now lung cancer is the most common cause of cancer mortality in both males and females and is the cause of 12.8% of cancer cases and 17.8% of cancer deaths worldwide (1). Lung cancer is the most common cancer (42.3% of all cancers) among males in Turkey. The annual age-standardized incidence rate was 61.6 per 100.000 in males, 5.1 per 100.000 in females in 1993-1994 (2).

The role of chemotherapy is well defined in first line setting after the meta-analysis of randomized trials in the treatment of inoperable non-small cell lung cancer (NSCLC) (3). Response rates and survival are increasing with the platinum combinations of these new agents. Chemotherapy is recommended in advanced NSCLC according to ASCO guidelines (4). Toxicity profiles of these new agents play an important role in the decision of chemotherapy.

Despite these improvements in chemotherapy drugs, recurrence is still inevitable. Although the role of second line chemotherapy has not been well defined, there is a need in many cases.

Docetaxel and pemetrexed are the two FDA approved chemotherapy agents for second line treatment of advanced NSCLC very recently (5,6). Treatment remains largely palliative in the second-line setting and there is a need to balance the benefits of palliative treatment against toxicity.

The role of second-line chemotherapy after initial treatment with a platinum-based regimen remains largely undefined. Most studies undertaken to date have been small phase II trials; drug dosages and schedules have varied. Activity of gemcitabine as a single agent has been found as effective as platinum combined chemotherapy in first line treatment of NSCLC (7). Effectiveness of gemcitabine in second-line setting was also investigated due to its activity and tolerability (8-10). Crino et al. reported that in the second-line setting in NSCLC patients response rate of gemcitabine was 19% and 45% of 1-year survival rate with tolerable toxicity (11).

Obtaining these data, we have started to perform gemcitabine in second-line setting in refractory or relapsing advanced NSCLC patients since 1999, in daily practice. Between August

1999 and August 2001, consecutive 34 patients with advanced NSCLC patients pretreated with cisplatin-based chemotherapy were treated with single agent gemcitabine. The aim of the retrospective study is to evaluate the effectiveness of gemcitabine as second line chemotherapy in these patients.

MATERIALS and METHODS

In our clinic, a software program titled Lung and Pleural Malignancies Patient Follow-up Program is used to keep patients records (12). Data obtained at the beginning and during the follow-up are recorded on this software program. In this retrospective analysis, we determined patients with NSCLC and received gemcitabine as second line from the soft ware program.

In daily practice of our clinic, second-line chemotherapy is performed according to the following criteria: Karnofsky performance status ≥ 70%, appropriate bone marrow reserve (leucocytes ≥ 3500, granulocytes ≥ 1500, Hb ≥ 10 g/dL, PLT ≥ 100.000), adequate kidney (serum creatinine level < 1.5 mg/dL) and liver (serum bilirubine level < 1.5 mg/dL, SGOT and SGPT value less than 3 times normal levels) functions. We don't give first or second line chemotherapy to patients with active serious infection, severe systemic diseases, pregnancy and lactation. All patients who evaluated for this retrospective analysis were suitable for these criteria and they had not taken gemcitabine in first-line chemotherapy.

Patients were given gemcitabine at a dose of 1250 mg/m^2 within 250 mL of isotonic solution on the 1st and 8th days, over 30 minutes. Chemotherapy was repeated in every 21 days.

Before each chemotherapy cycle, patient history, physical examination, Karnofsky performance status assessment, complete blood cell count, with differential and platelet count, and full chemistry profile, chest X-ray were obtained. Complete blood cell counts with platelet count was performed on day 8.

Dosage adjustment on day 8 was made on absolute granulocyte and platelet count. Full doses gemcitabine was performed if granulocyte count was ≥ 1500/mL and platelet count was ≥ 100.000/mL on day 8. If granulocyte count was of 1000 to 1500/mL or platelet count was of 75.000 to 100.000/mL, drugs were given 75% of the planned dose. The treatment was delayed by 1 week if granulocyte count was < 1000/mL and platelet count was < 75.000/mL on day of treatment. The dose was reduced 25% in case of febrile neutropenia or grade 4 thrombocytopenia or grade 3 non-hematological toxicity other than nausea/vomiting and alopecia.

Response was evaluated with chest X-rays or chest computed tomography after every two cycles of chemotherapy. Treatment was terminated in case of detection of radiological progression or worsening of symptoms in a stable disease, intolerable toxicity. Total number of 6 chemotherapy cycles was given to patients. Only in those cases that the response persists and improves at the 6th cycle, further cycles were given.

Response to therapy was assessed according to the World Health Organization (WHO) criteria; toxicities were evaluated during each course and graded according to the WHO toxicity scale. Complete response (CR) was defined as the complete disappearance of all tumor lesions for at least four weeks. Partial response (PR) was defined as a reduction of 50% in the product of the longest perpendicular diameters of the lesions. Progressive disease (PD) was defined as 25% increase in the product of the longest perpendicular diameters of the lesions or development of new lesions irrespective of response elsewhere. Stable disease (SD) was defined as the criteria, which fall in between PR and PD.

All clinical data were analyzed using the SPSS version 10.0 statistical software. The time to disease progression was measured from the date starting of second-line chemotherapy until the day of the first evidence of disease progression. Overall survival was measured from the date starting of second line chemotherapy to death or last contact. Kaplan and Meier curve were used to display the survival data. Cox Regression analysis was performed according to Forward Stepwise (Likelihood Ratio) method. Age, gender, Karnofsky performance status, tumor histology, stage were also analyzed.

RESULTS

According to software data between August 1999 and August 2001, 34 patients with advanced NSCLC treated with gemcitabine as second-line after cisplatin-based chemotherapy were evaluated for this study.

Median age was 50 years and squamous cell carcinoma was the most common malignancy (44.1%). Characteristics of patients were summarized in Table 1. Prior chemotherapy regimens and response rates are listed in Table 2. When we evaluate the response rates, no patient had a complete response, 7 (20.6%) patients had a partial response (Table 3). Table 4 shows previous chemotherapy situation and stages of responded patients to second line gemcitabine. When we evaluated the affect of response to previous chemotherapy on second-line chemotherapy, we found that the response to gemcitabine was 33% (3/9) among responded patients to first-line chemotherapy, 16% (4/25) among non-responded patients to first-line chemotherapy (p= 0.348).

Table 1. Characteristics of the patients.

	(n= 34)	
Characteristics	**No**	**%**
Sex		
Male	29	85.3
Female	5	14.7
Age, years		
Median	50	
Range	36-62	
Histology		
Squamus cell	15	44.1
Adenocarcinoma	7	20.6
Large cell	1	2.9
Unspecified NSCLC	11	32.4
Stage		
III	17	50
IV	17	50
KPS		
100	17	50
90	7	20.6
80	7	20.6
70	3	8.8

Table 2. Prior chemotherapy regimens and response rates.

Previous CT	Response of previous CT Responded	Non-responded	Total
CE	4 (25%)	12 (75%)	16 (47.1%)
CV	5 (33.3%)	10 (66.7%)	15 (44.1%)
MIC	0	2 (100%)	2 (5.9%)
CD	0	1 (100%)	1 (2.9%)
Total	9 (26.5%)	25 (73.5%)	34

CT: Chemotherapy, CE: Cisplatin, etoposide, CV: Cisplatin, vinorelbine, MIC: Mitomycine, ifosfamide, cisplatin, CD: Cisplatin, docetaxel.

Table 3. Response of second-line gemcitabine.

	Frequency	Percent
Complete response	0	0
Partial response	7	20.6
Stable disease	17	50.0
Progressive disease	10	29.4
Total	34	100.0

Table 4. Previous situation of responded patients to second line gemcitabine.

Patients responded to gemcitabine	Stage	Previous CT	Response to previous CT
Patient # 9	IV	CE	Negative
Patient # 11	IV	CE	Negative
Patient # 14	IIIB	CE	Positive
Patient # 18	IV	CE	Positive
Patient # 28	IIIB	CV	Positive
Patient # 30	IV	CE	Negative
Patient # 31	IIIB	CE	Negative

CT: Chemotherapy, CE: Cisplatin, etoposide, CV: Cisplatin, vinorelbine.

The median survival was 29 weeks (95% CI, 23.29 to 34.71 weeks). The 1-year survival probability was estimated at 26.5%. Median time to disease progression was 13.00 weeks (95% CI, 9.57 to 16.43 weeks).

According to Cox regression analysis; age, gender, performance status, tumor histology and stage did not show any significant prognostic importance on survival.

Total 119 chemotherapy cycles were performed on 34 patients, mean 3.5 (1-9 cycles). We observed grade 3 and 4 toxicities only in 2.5% of cycles (Table 5). Red blood cell transfusions were performed in 5 patients. Platelet transfusion was given in 1 patient. We did not observe any febrile neutropenic episode. There were 3 delaying on D1 and 5 on D8. There was one dose reduction on D8 in one patient once. We terminated chemotherapy in one patient for intolerable toxicity.

DISCUSSION

In this retrospective analysis, it was found that single agent gemcitabine as second line setting has 20.6% of response rate, 26.5% of 1-year survival probability and low toxicity rate.

Currently there is insufficient data regarding the use of gemcitabine in second-line applications. Crino et al. prescribed 83 patients with non-small cell carcinoma of the lung who did not respond to first line chemotherapy or had recurrence 1000 mg/m^2 gemcitabine to be given on days 1, 8 and 15 and they reported a partial response in 16 patients (19%), with a median survival of 34 weeks and 1-year-survival of 45% (11). In the same study, the authors reported that 11 of the 16 patients who responded to gemcitabine also responded to first line chemotherapy, only one patient who was resistant to first line chemotherapy responded to the treatment and 1 year survival among patients who did not respond to chemotherapy was 15% (11). Only 3 of the 7 cases who responded to the treatment in our study also responded to the first line chemotherapy and four patients did not. Similar response rates are observed in both studies while Crino found a higher survival than we did.

Sculier and colleagues administered gemcitabine as a second-line chemotherapy to 65 patients. Four patients responded to the treatment, two of which had a partial response to previous chemotherapy and 2 were stable, with a survival of 17 weeks (9). Our study, together with these two studies, indicates that response to first-line chemotherapy is not a sufficient data while deciding which patients to include in second-line chemotherapy. We found similar results in our study. However, due to limited number of cases, statistical analysis will not give a permission the most correct results. Despite of this point, when we evaluated the effect of response to previous

Table 5. Toxicity profile of patients.

		(n= 119 cycles)	
Toxicity		**No**	**%**
Leucopenia	Grade 1-2	24	20.2
	Grade 3	2	1.7
Neutropenia	Grade 1-2	22	18.5
	Grade 3-4	3	2.5
Thrombocytopenia	Grade 1-2	9	7.6
	Grade 3-4	2	1.7
Anemia	Grade 1-2	23	19.3
Nausea/vomiting	Grade 1-2	24	20.2
	Grade 3-4	3	2.5
Stomatit	Grade 1-2	4	3.4
Diarrhea	Grade 1-2	6	5
Constipation	Grade 1-2	7	5.9
Fever	Grade 1-2	2	1.7
Allergy	Grade 1-2	5	4.2
Alopecia	Grade 1-2	6 (patients)	
ALT elevation	Grade 1-2	1	0.8

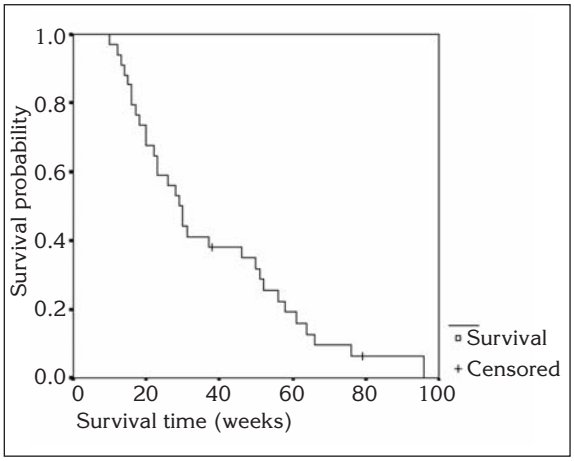

Figure 1. Survival of patients.

chemotherapy on second-line chemotherapy, there was no significant difference between the responded or non-responded patients to previous chemotherapy (33.3%; 16%). According to these studies, the response to first-line chemotherapy is not a sufficient data while deciding which patients to include in second-line chemotherapy.

Reddy et al. conducted a study on 27 patients and used 1000 mg/m^2 gemcitabine on days 1 and 8 as a second-line and reported a response rate of 7% (13). Efficacy of the drug was low due to relatively smaller doses of gemcitabine being used.

Van Putten et al. used 1000 mg/m^2 gemcitabine on days 1, 8 and 15 as a second-line on 80 patients (51 of them had curative radiotherapy previously) and reported that the response rate was 13% and quality of life improved in 30%. Authors have also argued that having curative radiotherapy before the treatment might have contributed to the low response rate (14). Cho et al. carried out a similar second-line study on 27 patients which they used 1000 mg/m^2 gemcitabine on days 1, 8, 15 and found that 18.5% responded to the treatment and median survival was 38 weeks (15).

Statistically significant effects of age, sex, performance state or the population could not be shown in a Cox regression analysis exploring the factors affecting the second-line chemotherapy. When we compared the response rates of first-line and second-line chemotherapy protocols, we found that 6 of the 16 patients (37.5%) who had cisplatin-etoposide, and only one of 15 patients (6.7%) who had cisplatin-vinorelbine as a first-line treatment responded to second-line gemcitabine.

With respect to the ratios of toxicity, Van Putten et al. grade 3-4 neutropenia and thrombocytopenia in 9% of the cases (14). Gillenwater et al., on the other hand, used 1250 mg/m^2 gemcitabine on days 1, 8 and 15 and reported that the rate of response was 6.5% and they had to make toxicity related dose adjustments in 8% of the cases (10). However, the fact that all of the patients in that study were stage IV can explain the low response and high toxicity rates. Sculier et al. reported that they reduced the dose in 25 patients due to toxicity and postponed the treatment 9 times in a study they conducted on a total of 77 patients which 96% of them were stage IV (9). Crino et al. reported grade 3 leukopenia in 6%, grade 4 leukopenia in 1% and grade 3 thrombocytopenia in 7% of their cases (11). In the present study, 50% of the cohort was stage IV, the ratios of grade 3-4 neutropenia or nausea/vomiting were 2.5%, and thrombocytopenia was 1.7%. The dose needed to be reduced only once, on day 8, and treatment had to be postponed 3 times on day 1 and 5 times on day 8. Our toxicity rates were relatively lower than other studies. This difference may be due to the facts that patients were treated on days 1 and 8, 91.2% of the patients had a KPS of 80% or over, or low percentage of stage IV patients. Indeed Cho and colleagues encountered grade 3 neutropenia and thrombocytopenia in 1%, grade 3 anemia in 3% but no grade 4 toxicity during a study in which stage IV patients comprised 48% of the study sample (15).

A phase II study by Fossella et al. reported 21% partial response with docetaxel as a second-line and 41% 1-year survival (16). However, Shepherd et al's phase III study that used docetaxel in second-line reported a 7% response, with 29% 1-year-survival, but the quality of life was better than the best supportive care group (17). Alexopoulos et al. used docetaxel as second-line in 60 patients and reported response in 25%, 1 year survival in 23%, grade 3-4 neutropenia in 18-23%, grade 2 peripheral neuropathy in 15% and hospitalization due to febrile neutropenia in 30% of the cases (18). Though response to docetaxel was high, so were the rates of toxicity.

Two separate studies that paclitaxel was used reported 3% and 30% of partial response (19,20). The response rates of two studies on second-line treatment of NSCLC with vinorelbin as a single agent were 0% (21,22). Santoro and colleagues, on the other hand, reported a success rate of 20% with vinorelbine, but did not provide any data on the median survival and 1-year-survival (23).

In conclusion, this study shows that 1250 mg/m^2 gemcitabine is moderately effective, well tolerated agent for the second-line treatment of NSCLCs. Even though this is a retrospective analysis, data support the view that gemcitabine can be kept in mind among other second-line chemotherapy choices.

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