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ORIGINAL ARTICLE

Biweekly cisplatin and gemcitabine with two different doses in non small cell lung cancer patients: A retrospective single-center experience

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Summary

Purpose: *Non-small-cell lung cancer (NSCLC) constitutes 80-85% of all lung cancers. Patients with advanced-stage NSCLC may benefit from chemotherapy. Gemcitabine and cisplatin is a well-established therapy for this malignancy. Recently, biweekly administration is becoming more acceptable, but the most effective and tolerable dose remains unclear. The purpose of this study was to compare the toxicity and efficacy of 1000 mg/m² gemcitabine (GEM 1000) and 1500 mg/m² gemcitabine (GEM 1500) in combination with 50 mg/m² cisplatin.*

Methods: *Gemcitabine was administered at a dose of 1000 or 1500 mg/m² with cisplatin administered at a dose of 50 mg/m² on day 1. The treatment was repeated every 2 weeks for a total of 4 courses. Response rates, progression-free survival (PFS), overall survival (OS) and toxicities were assessed.*

Results: *114 patients with IIIB and IV stages of NSCLC were included. Seventy two patients (63%) received GEM 1000 and 42 (37%) received GEM 1500. The overall reponse rate (ORR), PFS and OS were 24%, 6 months and 13 months respectively in the GEM 1000 group and 36%, 6 months and 15 months in the GEM 1500 group, respectively. Grade 3-4 neutropenia and thrombocytopenia were observed in 4% of the GEM 1000 group and 9% of the GEM 1500 group (p=0.41).*

Conclusion: *Biweekly administration of GEM 1000 and 1500 is a well tolerated regimen. Although the GEM 1000 group showed a lower response rate than the GEM 1500 group, PFS and OS were similar.*

Key words: *biweekly regimen, chemotherapy, cisplatin-gemcitabine, lung cancer, non-small cell*

Introduction

Lung cancer is broadly divided into small and non small cell cancer. NSCLC constitutes 80-85% of all lung cancers [1]. Approximately 80% of patients have either stage III (approximately 44%) or stage IV disease (approximately 35%) at the time of diagnosis [2]. Prognosis in advanced NSCLC patients is still very poor [3]. Patients in advanced stages (stages IIIB/IV) may benefit from chemotherapy [4]. Platinum-based doublet chemotherapy is the standard of care for patients with advanced NSCLC [5]. Recently, cisplatin with one of the third generation agents including paclitaxel, docetaxel, gemcitabine, irinotecan and vinorelbine combinations showed improved OS compared to cisplatin with second generation agents such as vindesine or etoposide in patients with advanced NSCLC [6].

In advanced NSCLC, cisplatin or carboplatin with vinorelbine, gemcitabine or taxanes combina-

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tions are most effective regimens [7-11]. Cisplatin and gemcitabine combination is one of the recommended standard regimens.

Gemcitabine is a third generation chemotherapeutic agent and has a wide-spectrum of antitumor activity [12]. Gemcitabine-containing regimens showed superior efficacy and lower toxicity compared with other regimens in several studies, so it should rather be incorporated in combinations for advanced NSCLC [8,12-14].

Gemcitabine and cisplatin have a synergistic effect [15] and this combination is used for several solid malignancies, including NSCLC, ovarian cancer and head and neck squamous cell carcinoma [16-18].

At first, gemcitabine was given on days 1, 8 and 15. every 4 weeks but with high incidence of thrombocytopenia and neutropenia [19,20]. Three-weekly regimen had a more acceptable adverse effects profile when compared with the 4-weekly schedule [21]. Three-weekly cisplatin and gemcitabine combination is a well known and commonly used regimen as first-line treatment of NSCLC [9,12,22,23].

Recently, biweekly regimen is becoming more acceptable, yet the most effective and tolerable dose is unclear. The purpose of this study was to compare the toxicity and efficacy of GEM 1000 and GEM 1500 in combination with 50 mg/m^2 cisplatin.

Methods

Study population and data collection

Between January 2002 and December 2016, all NSCLC patients who received biweekly cisplatin and gemcitabine as first-line chemotherapy at the Erciyes University, Department of Medical Oncology were retrospectively reviewed. Included were patients with histologically proven NSCLC with clinical stages IIIB and IV, and who received at least two cycles of cisplatin-gemcitabine protocol as their first-line treatment. Data were collected from the hospital's patient records, including patient characteristics, metastatic sites, tumor stage, tumor response and date of death. Tumor response evaluation was based on computed tomography at each of the 4 cycles according to WHO response evaluation criteria.

Treatment

Cisplatin was administered at a dose of 50 mg/m^2 on day 1 with gemcitabine administered at a dose of 1000 mg/m^2 or 1500 mg/m^2 on day 1 too according to the attending clinician's decision. The treatment was repeated every 2 weeks for a total of 4 courses. Toxicity was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0).

Statistics

Gemcitabine 1000 and 1500 mg/m^2 groups were compared each other. Median, min, max and number of patients were defined. Normality was determined with Kolmogorov-Smirnov test. Student's *t*-test was used for parametric variables, Mann-Whitney U test was used for nonparametric variables and chi-square test was used for categorical data to describe the sample and compare GEM 1000 and GEM 1500 groups. PFS was calculated from the date of chemotherapy initiation to the date of progression. OS was defined from the date of chemotherapy initiation to the date of death or last known contact. Tumor response was evaluated according to WHO response criteria. Response was defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The primary endpoint of this study was PFS and ORR, while the secondary endpoints were OS and adverse events. PFS and OS curves were generated using the Kaplan -Meier method, and log-rank test was used for intergroup comparisons. A p value <0.05 was regarded as statistically significant. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

Results

Patient characteristics

One hundred fourteen patients diagnosed with stage IIIB and IV NSCLC were included in the study. The majority of patients were male (n=104) and the median age was 59 years (range 28-82). Eighty eight percent of patients had stage IV (n=100), and the remaining 14 had stage IIIB. One hundred four patients had ECOG PS 0-1 (91%), and 10 patients had ECOG PS 2. All patients with ECOG 2 performance status received gemcitabine at a dose 1000 mg/m^2 (Table 1).

Seventy two patients (63%) received gemcitabine at a dose of 1000 mg/m^2 and 42 (37%) received 1500 mg/m^2. In the GEM 1000 group the median age was 55 years and in the GEM 1500 group the median age was 61 years (p=0.02). In the GEM 1000 group 62 patients (86%) had adenocarcinoma and 10 (14%) epidermoid carcinoma. In 1500 mg group 5 (12%) patients had adenocarcinoma, 34 (81%) had epidermoid carcinoma and 3 patients (7%) were diagnosed with other histological types (Table 1). The gemcitabine dose intensity of the patients that received 1000 mg/m^2 it was 497.85 (99.5% of the planned dose; mg/m^2/week) and for those that received 1500 mg/m^2 it was 739.11 (98.5% of planned dose; mg/m^2/week). The cisplatin dose intensity of the GEM 1000 was 24.96 (99. 8 % of the planned dose; mg/m^2/week) and for the GEM 1500 it was 24.49 (97.95 of planned dose; mg/m^2/week) (Table 1).

Table 1. General patient and disease characteristics

Characteristics	*Adenoca n=67 (60%) n (%)*	*Squamous n=44 (40%) n (%)*	*p value*	*1000 mg/m² n=72 (63%) n (%)*	*1500 mg/m² n=42 (37%) n (%)*	*p value*	*Total n=114 n (%)*
Age, years (median, min-max)	55 (28-82)	62 (43-78)	<0.001	55 (28-82)	61 (43-78)	0.02	59 (28-82)
Sex							
Male	59 (88)	42 (95)	0.31	63 (88)	41 (98)	0.09	104 (91)
Female	8 (12)	2 (5)		9 (12)	1 (2)		10 (9)
Stage			0.35			0.02	
3B	2 (3)	12 (27)		5 (7)	9 (21)		14 (12)
4	65 (97)	32 (73)		67 (93)	33 (79)		100 (88)
ECOG performance status			1			0.01	
0-1	58 (87)	43 (98)		62 (86)	42 (100)		104 (91)
2	9 (13)	1 (2)		10 (14)	0		10 (9)
Histological subtype							
Adenocarcinoma				62 (86)	5 (12)		67 (59)
Squamous				10 (14)	34 (81)		44 (39)
Others					3 (7)		3 (2)
Metastatic area							
Lymph nodes	24 (36)	30 (68)		28 (39)	29(69)		57 (50)
Pleura	13 (19)	1 (2)		13 (18)	1 (2)		14 (12)
Liver	9 (13)	3 (7)		9 (13)	3 (7)		12 (11)
Surrenal	18 (27)	6 (14)		19 (26)	7 (17)		26 (23)
Brain	20 (30)	5 (11)		17 (24)	8 (17)		25 (22)
Bone	43 (64)	12 (27)		43 (60)	13 (31)		56 (49)
Bone marrow	1 (2)	0		1 (1)	0		1 (1)
Contralateral lung	20 (30)	18 (41)		23 (32)	15 (36)		38 (33)
Number of metastatic areas							
1	18 (27)	20 (46)		22 (31)	16 (38)		38 (33)
2	28 (42)	17 (39)		30 (42)	18 (43)		48 (42)
≥3	21 (31)	7 (15)		20 (27)	8 (19)		28 (25)
Number of visceral metastases							
0	14 (21)	18 (41)		19 (26)	14 (33)		33 (29)
1	32 (48)	18 (41)		31 (43)	21 (50)		52 (46)
2	16 (24)	8 (18)		17 (27)	7 (17)		24 (21)
≥3	5 (7)	0		5 (4)	0		5 (4)
Tumor response							
PD	18 (27)	10 (23)		20 (28)	11 (26)		31 (27)
SD	31 (46)	20 (46)		35 (49)	16 (38)		51 (45)
PR	18 (27)	14 (31)		17 (24)	15 (36)		32 (28)
Toxicity (grade 3-4)							
Neutropenia	4 (6)	2 (5)		3 (4)	3 (7)		6 (5)
Trombocytopenia	0 (0)	1 (2)		0 (0)	1 (2)		1 (1)
Dose intensity (mg/m²/week)							
Gemcitabine (%)				497.8 (99.5)	739.1 (98.5)		
Cisplatin (%)				24.9 (99.8)	24.4 (97.9)		

Response and survival

The overall reponse rate for the 114 patients was 28% with 32 PRs. No patient achieved CR. Fifty one patients (45%) showed SD and 31 (27%) PD. ORR was 29% in stage IIIB patients and 29% in stage IV patients. In the GEM 1000 group the ORR was 24% and in the GEM 1500 group it was 36% (Table 1).

In the GEM 1000 patients PFS was 6 months (95% CI, 4.68-7.32) and in the GEM 1500 it was 6 months (95% CI, 4.83-716; log rank, n=0.60) (Figure 1). In the adenocarcinoma group PFS was 6 months (95% CI, 4.75-7.24) and in the squamous cell cancinoma group it was 6 months (95% CI, 4.72-7.27; log rank, n=0.11) (Figure 2).

In the GEM 1000 group the median OS was 13 months (95% CI, 10.22-15.77) and in the GEM 1500 group it was 15 months (95% CI, 10.82-19.17; log rank, p=0.48) (Figure 1). In the adenocancinoma patients OS was 15 months (95% CI, 11.65-18.34) and in the squamous cell cancinoma it was 13 months (95% CI, 8.78-15.21; log rank, p=0.74) (Figure 2).

Toxicity profile

In the GEM 1000 group grade 3-4 neutropenia was observed in 3 (4%) cases while no grade 3-4 thrombocytopenia was noticed. In the GEM 1500 group grade 3-4 neutropenia was observed in 2 (7%) cases and grade 3-4 thrombocytopenia in 1 (2%;p=0.41;Table 1).

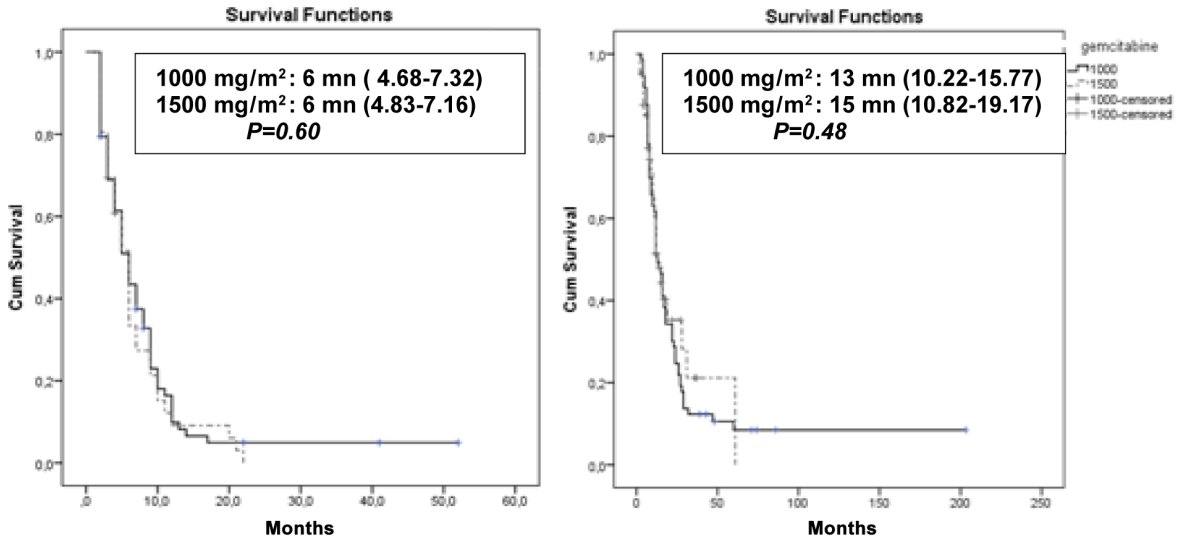

Figure 1. Progression-free survival (left) and overall survival (right) in 1000 and 1500 mg/m² dose gemcitabine groups. mn: months.

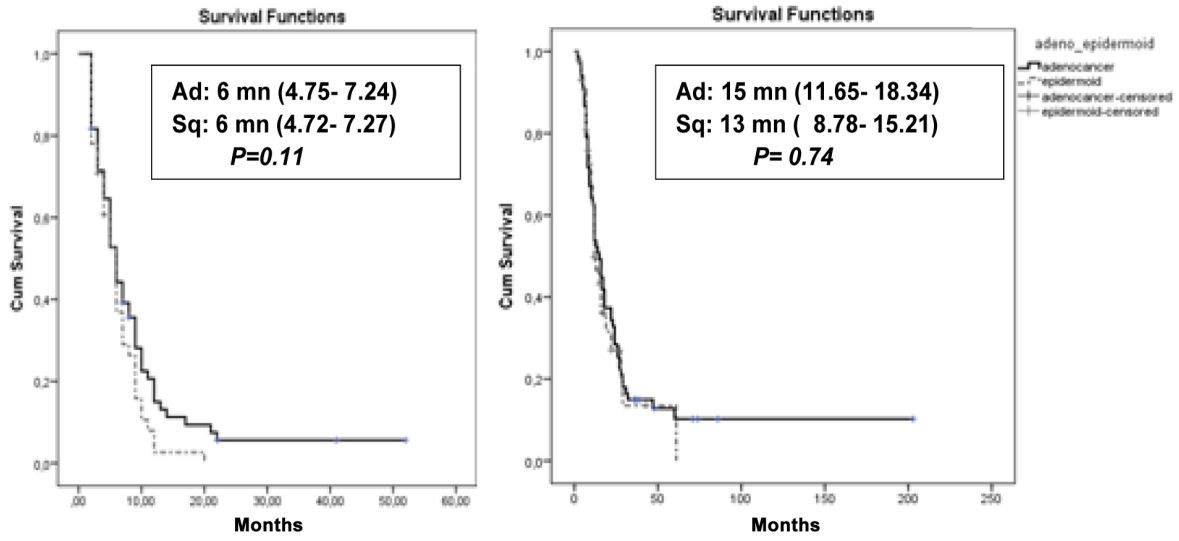

Figure 2. Progression-free survival (left) and overall survival (right) in adenocancinoma (Ad) and squamous cell (Sq) carcinoma group. mn: months.

In the adenocancinoma group grade 3-4 neutropenia was observed in 4 (6%) patients with no grade 3-4 thrombocytopenia, while in the squamous cell cancer group grade 3-4 neutropenia was observed in 2 (5%) cases and 3-4 thrombocytopenia in 1 (2%; p=0.85; Table 1).

Discussion

The optimal schedule and dose of administration for gemcitabine in combination with cisplatin is still unclear. In this study we compared 1000 mg/m^2 with 1500 mg/m^2 gemcitabine in combination 50 mg/m^2 cisplatin.

Platinum-based combination therapy is the standard treatment in NSCLC. In a phase III trial from Sandler et al. cisplatin alone and cisplatin/gemcitabine (CG) combination were compared with each other. Cisplatin was given at 100 mg/m^2 i.v. on day 1 of a 28-day cycle and gemcitabine at 1000 mg/m^2 was given i.v. on days 1, 8, and 15 of a 28-day cycle [2]. This study demonstrated that cisplatin and gemcitabine combination had a statistically significant effect on response rate, OS and PFS compared with single-agent cisplatin. A phase II trial reported the comparison of results of 3-weekly with 4-weekly CG regimen [21]. Patients in the 3-weekly regimen had lower adverse effects but the response rate was similar compared with the 4-weekly regimen (response rate: 3-weekly= 39%, 4-weekly= 38%).

Recently, the biweekly regimen is becoming more preferred in advanced NSCLC. In a study by Vivanco et al. 49 patients received biweekly cisplatin 50 mg/m^2 and gemcitabine 2500 mg/m^2 on days 1 and 15 every 28 days [22]. In this trial ORR was 38%, median OS 48 weeks and median PFS 26 weeks.

We compared GEM 1000 and GEM 1500 in combination with cisplatin 50 mg/m^2 in a biweekly schedule. ORR was lower in the GEM 1000 group compared with the GEM 1500 group, but PFS and OS were similar in both groups. Although the patients in the GEM 1500 group were older than those in the GEM 1000 group, stage and performance status favored the GEM 1500 group. And in the GEM 1500 group brain, liver, pleura, bone marrow metastasis and metastatic sites were fewer than in the other group. In a study with patients having 4 or more metastases, low performance status and liver metastasis were defined as poor prognostic factors, but histology wasn't related with poor prognosis [23]. Difference in ORR can be related with this favourable characteristic. Also the two groups had different histological characteristics. In the GEM 1500 group most of the patients had squamous cell carcinoma but in the GEM 1000 group most patients had adenocarcinoma. Hoang et al. analyzed the results of a phase 3 (ECOG1594) study that included 1139 patients and showed that in the cisplatin/gemcitabine group, squamous cell carcinoma and large cell carcinoma patients had a numerically longer OS compared to the other histological subtypes but without significant difference [24].

In our study there were 67 (59%) patients with adenocarcinoma and 44 (39%) with squamous cell carcinoma, without statistical difference in PFS and OS. In the ECOG1594 study PFS was 4.7 months in the non squamous group and 5.5 months in the squamous group, while OS was 10.4 months in the non squamous group and 10.8 months in the squamous group. Both adenocancinoma and squamous cell cancer groups in our study showed longer PFS and OS than the ECOG1594 study. In our study there were no large cell carcinoma patients but our patient population had poorer characteristics compared to this study. For example, in our study brain metastases were higher (22 vs 12%) and ECOG performance status was 2 in 9% of the patients in our study and 5.5% in that study.

In the GEM 1500 group grade 3-4 neutropenia and thrombocytopenia were higher than in the GEM 1000 group, as would be expected. Soto Parra et al. demonstrated that in the 3-week schedule there was more grade 3-4 hematological toxicity than in the 4-week schedule [21]. Vivanco et al. reported that 8% of the patients developed grade 3-4 neutropenia and thrombocytopenia in a biweekly regimen [22]. They administered gemcitabine at a dose of 2500 mg/m^2. This toxicity is similar with our GEM 1500 group, but higher than the GEM 1000 group. Their gemcitabine dose intensity was higher than our GEM 1500 group but cisplatin dose intensity was lower than our GEM 1500 group and our planned dose given was higher than in that study. Although in the GEM 1500 group grade 3-4 thrombocytopenia and neutropenia were similar with that study, our PFS and OS was numerically higher compared with that study and maybe this could be related with the higher cisplatin dose. It is possible that our gemcitabine dose allows high planned dose of cisplatin. In a study from Korea the schedule was 1250 mg/m^2 gemcitabine every 21 days with 75 mg/m^2 cisplatin. Grade 3-4 neutropenia was seen in 24% of the patients and grade 3-4 thrombocytopenia in 7.8% [25]. Ma et al. reported their study in NSCLC patients who were administered cisplatin 80 mg/m^2 on days 2-4 and gemcitabine 1250 mg/m^2 on days 1 and 8 every 3 weeks in the adjuvant setting. The authors observed grade 3/4 thrombocytopenia and neutropenia in 36% of the patients [26]. Both gemcitabine and cisplatin dose intensity were higher than in our study.

In the present study we demonstrated that biweekly GEM 1000 and 1500 dose of gemcitabine was well-tolerated. Although the GEM group had a lower response rate than the GEM 1500, PFS and OS were similar. Gemcitabine 1500 mg/m^2 in a biweekly administration had produced favourable results, and 1000 mg/m^2 gemcitabine in a biweekly administration is an alternative option for patients who have poor performance status and older age.

Limitations

In this retrospective study we reviewed only neutropenia and thrombocytopenia in a small number of patients. Other adverse effects must be reviewed prospectively in large-cohort studies.

Conflict of interests

The authors declare no conflict of interests.

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