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## Original Article

# gemcitabine-docetaxel versus gemcitabine - cisplatin as first-line therapy in patients with advanced non-small cell lung cancer

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**Purpose:** was to compare the gemcitabine-docetaxel combination with the standard cisplatin- gemcitabine regimen in patients with advanced or metastatic Non-small cell lung cancer (NSCLC) in a phase III study.
**Patients and Methods:** From Nov. 2010 to Jun. 2013, all patients with TNM stage IIIB or IV NSCLC who met the eligibility criteria were enrolled in this study. They were randomized into two arms: Arm 1 (gemcitabine-cisplatin (GC) arm) and Arm 2 (gemcitabine-docetaxel (GC) arm). In both arms, gemcitabine was administered at the dose of 1000 mg/m2 on days 1 and 8 every 21 days. In GD Arm, docetaxel 75 mg/m2 was administered intravenously on day 1. In GC Arm, cisplatin 75 mg/m2 was administered intravenously on day 1. Patients with stable disease (SD) received a maximum of six cycles; and patients with a complete response or partial response (PR) after the sixth cycle received 2 additional cycles.
**Results:** Ninety one patients were enrolled in this study, of which 45 and 46 were randomized to the GC and GD arms, respectively. The median progression free survival (PFS) was 6.5 months for GD arm vs. 6.8 months for GC arm, ($P$=0.772). Median Overall survival (OS) was 8.5 months for the GD group and 8.9 months for the GC group, ($P$=0.945). There was also no difference in OS between the two treatment arms with regards the primary stratification factor of histology ($P$= 0.922). No CR cases were recorded in either group. PR rate was 43.5% in the GD arm compared with 46.7% patients in the GC arm.
Chemotherapy-related toxicities including hematologic, nausea and vomiting and nephrotoxicity were more common in the GC group. There were no toxicity-related deaths.
**Conclusion:** The results presented in this study suggest that gemcitabine-docetaxel (GD) combination is equally active to standard cisplatin-gemcitabine (GC) regimen when used as first-line therapy in the treatment of patients with stage IIIB/IV NSCLC. The more favorable toxicity profile of GD supports its use as first-line chemotherapy, especially in patients who cannot tolerate cisplatin.

**Key words:** advanced non-small cell lung cancer, chemotherapy, cisplatin and docetaxel
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Original Article

## INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide in men, and second most common in women. Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths[1]. Non–small-cell

lung cancer (NSCLC) represents more than 80% of lung cancer diagnoses and has an overall 5-year survival rate of approximately 16%, which decreases precipitously among patients diagnosed with late stage disease[2].

Despite enthusiasm for the use of molecular testing and molecularly targeted agents in patients with advanced non–small cell lung cancer (NSCLC), most patients are not candidates for upfront treatment with molecular agents. Moreover, many candidate patients can't afford the vastly increased cost of such novel agents. Chemotherapy therefore remains the first-line treatment for most patients with stage IV non–small cell lung cancer (NSCLC)[3].

Multiple individual randomised studies and several meta-analyses have shown a survival benefit for platinum-based chemotherapy compared with best supportive care in patients with good performance status[4,5], but at the cost of severe toxicities. Combinations with better toxicity profile but with equal or improved efficacy are eagerly needed. Nonplatinum combinations have been tested and are considered alternative regimens for those who cannot tolerate platinum-based chemotherapy. Among these combinations, the combination of gemcitabine and docetaxel has emerged as one of the most promising, showing equivalent efficacy with, and less toxicity than, cisplatin-based chemotherapies[6].

Gemcitabine (2′-deoxy-2′,2′-difluorocytidine monohydrochloride) is a nucleoside antimetabolite against deoxycytidine. It is intracellularly metabolized to gemcitabine triphosphate, which inhibits DNA synthesis, and has shown potent cytocidal activity against solid tumors[7]. Docetaxel, an antineoplastic agent that acts on microtubules to promote formation of abnormal microtubule bundles, has also shown cytotoxicity[8]. Gemcitabine and docetaxel have different mechanisms of action, but by combining them, there is the potential of synergistic antitumor activity[9].

Aim of the study was to compare the gemcitabine-docetaxel combination with the cisplatin- gemcitabine regimen as first-line therapy in patients with advanced or metastatic NSCLC in a phase III study.

## PATIENTS AND METHODS

Between Nov. 2010 till Jun. 2013, patients with stage IIIB or IV NSCLC presenting at Assiut University Oncology Department were entered in this prospective phase III randomized trial. Sample size was based on the prevalence of advanced NSCLC in Assiut Clinical Oncology department. An accrual rate of 45 patients/year was projected and a total sample size was 90 patients.

### Eligibility Criteria

Patients with histologically or cytologically confirmed unresectable TNM stage IIIB or IV NSCLC (according to AJCC cancer staging system 7th edition (2010)) who met the following criteria were eligible for the study: with no prior chemotherapy; with at least one measurable lesion that could be accurately measured in at least one dimension; aged 20–74 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; a life expectancy of at least 3 months; and adequate organ functions as indicated by white blood cell count ≥4.0 × 109/l, platelets ≥100 × 109/l, hemoglobin ≥9.5 g/dl, aspartate aminotransferase/alanine aminotransferase ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 times the upper limit of normal, serum creatinine ≤ the upper limit of normal.

Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis, or grade 2–4 peripheral neuropathy or marked edema. Additional exclusion criteria included: superior vena cava syndrome; symptomatic brain metastasis; or history of serious drug allergy.

All patients who entered into this study were required to give written informed consent. The trial was approved by the ethics committee of the Faculty of Medicine, Assiut University.

### Study Design and Treatment

Patients were randomized by simple randomization into two arms: Arm 1 (GC arm) and Arm 2 (GD arm). In both arms, gemcitabine was administered at the dose of 1000 mg/m$^2$ in a 30-min infusion on days 1 and 8 every 21 days. In GD Arm, docetaxel 75 mg/m$^2$ was administered intravenously over at least 1 h on day 1. Gemcitabine was given immediately after the docetaxel infusion. In GC Arm, cisplatin 75 mg/m$^2$ was administered intravenously over 2 h on day 1. All patients received ondansetron 8mg and dexamethasone 8mg intravenously as premedication. Those receiving docetaxel received dexamethasone 8mg orally BID the day before, and the day after and 12 hours after docetaxel infusion. Those receiving cisplatin were prehydrated with 1000 mL NS over 1 hour, then given Cisplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 2 hours.

Patients with stable disease (SD) received a maximum of six cycles; and patients with a complete response or partial response (PR) after the sixth cycle received 2 additional cycles.

### Dose Modifications

Administrations of chemotherapeutic drugs on day1 were delayed for patients with an absolute neutrophil count <1.5 × 109/l, a platelet count <100 × 109/l, or any grade 3/4 non-hematologic toxicities. When gemcitabine was given on day 8 of both arms, exceptions included leukopenia <2.0 × 109/l and an absolute neutrophil count <1.0 × 109/l, a platelet count <70 × 109/l, or any grade 3/4 non-hematological toxicities. In subsequent cycles, doses of both drugs of both arms were reduced by 25% if chemotherapy-induced febrile neutropenia or grade 4 thrombocytopenia occurred. The doses of docetaxel and cisplatin were reduced by 25% for grade 2 or 3 neurotoxicity. Dose reductions were maintained for all subsequent cycles.

### Baseline and Treatment Assessment

Before the day of starting the study treatment, assessments at baseline included doing physical examination in addition to history taking, grading performance status, tumor measurements by chest X-ray and computed tomography (CT) scan of the neck, chest and abdomen, and doing CBC, blood chemistries, creatinine clearance and electrocardiography (ECG). Bone scan and MRI brain were also done for all patients.

Assessment of patients' complaints, performance status, physical examination, hematology, and blood chemistries were obtained days 1 and 8 of each cycle. Adverse events were estimated according to National Cancer Institute–Common Toxicity Criteria version 2.0.

Lesions were measured after 1st cycle by chest x-ray and each cycle if they were assessable by physical examination. All patients were evaluated by computed tomographic scans of the chest and abdomen after every three courses.

Standard WHO response criteria[10] were used to define the tumor response. A complete response (CR) required the disappearance of all measurable and assessable disease in all disease sites, including no new lesions. A partial response (PR) required ≥50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Both CR and PR had to be maintained for more than 4 weeks. Stable disease was defined as a decrease of less than 50% as well as an increase of less than 25% in the sum of the products of measurable lesions without the appearance of any new lesion. Progressive disease was defined as an increase of ≥25% in the sum of the products of the measurable disease or the appearance of any new lesions or the reappearance of any lesion that had disappeared. Patients with disease progression, either primary or after initial response were assessed for ECOG PS and organ functions. Those who still had ECOG PS ≤ 2 and adequate organ functions were offered 2nd line single agent chemotherapy (carboplatin AUC 5 for Arm 1 patients and Docetaxel 75mg/m$^2$ for Arm 2 patients). Other patients received best supportive care.

The primary objective of the study was to compare overall survival (OS); secondary objectives included evaluation of response rates, progression-free survival (PFS), and toxicity on both study arms.

**Statistical methods of analysis:**

Overall survival and progression free survival were estimated by Kaplan Meier methods. Overall survival was estimated from the date of treatment start till death or last follow-up visit. Progression-free survival (PFS) was defined as the time elapsed between treatment initiation and tumor progression or death from any cause.

Tests of significance: T test and Chi-square were used to study significance differences between variables.

**P*.value >0.05 not significant. **P*. value ≤ 0.05 significant.

Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL).

## RESULTS

From Nov. 2010 to Jun. 2013, 91 patients were enrolled in this study, of which 45 and 46 were randomized to the GC and GD arms, respectively. Patient demographics and clinical characteristics are presented in Table 1. Both arms were balanced for age, sex, smoking habits, disease stage, and histologic subtype and grade. Of the whole series, more than 80% of patients had stage IV disease. The most common histologic subtype was adenocarcinoma (GD, 53.3% and GC, 54.3%).

Overall, 37 of 91 patients (40.7%) completed the six cycles of treatment (GD, 17/45 [37.8%] and GC, 20/46 [43.5%]). Another 31 patients received only four cycles of chemotherapy (GD, 14/45 [31.1%] and GC, 17/46 [37 %]). The remaining patients received a range of 1-3 cycles (GD, 14/45 [31.1%] and GC, 9/46 [19.6%]). The main cause of treatment withdrawn was progression of disease (28.9% and 30.4% in arm GD and GC respectively) while early stopping for serious adverse events occurred in 10.9% and 17.6% in arm GD and GC, respectively. In arm GD, 33.3 % of cycles were delayed for haematological or nonhaematological toxicities and in 16.7% of the cycles the doses of both drugs were reduced. In arm GC treatment was delayed in 26.7% of cycles with dose reduction of both drugs in 17.5% of cycles.

**Outcome**

With a median follow-up 17 months, the median PFS was 6.5 months (S.D. = 0.472(5.575 7.425–)) for GD group and 6.8 months (S.D. = 0.302(6.2087.392 –)) for GC group (Figure 1). There was no statistically significant difference in PFS between the two treatment arms (*P*=0.772). Median OS was 8.5 months (S.D. = 0.421 (7.6479.326 –)) for the GD group and 8.9 months (S.D. = 0.674(7.580 10.220 —)) for the GC group, (*P*=0.945) (Figure 2).

With stratifying patients according to the histopathological diagnosis into squamous and non-squamous subgroups, there was also no difference in OS between the two treatment arms (Fig. 3 A & B) (*P*= 0.922).

No complete response cases were recorded in either group. Partial response rate was 43.5% in the GD group compared with 46.7% patients in the GC group (Table 2).

Only 9 patients (20%) of GD group and 8 patients (17.4%) of GD group received second-line chemotherapy. Other patients received best supportive care on disease progression.

**Toxicity**

A summary of grade 3/4 toxicities by treatment arm is presented in Table 3. The most common grade 3/4 toxicities were hematologic in nature, with thrombocytopenia, neutropenia, and leukopenia being more prevalent in GC Arm than in GD Arm but the differences are not statistically significant. Vomiting

(17.6% and 10.9% for GC and GD, respectively) was the most common nonhematologic grade 3/4 toxicities. Grade 3/4 peripheral sensory neuropathy occurred at a higher rate in the GD group than in the GC group (8.7% versus 4.4%). There was no toxicity-related death.

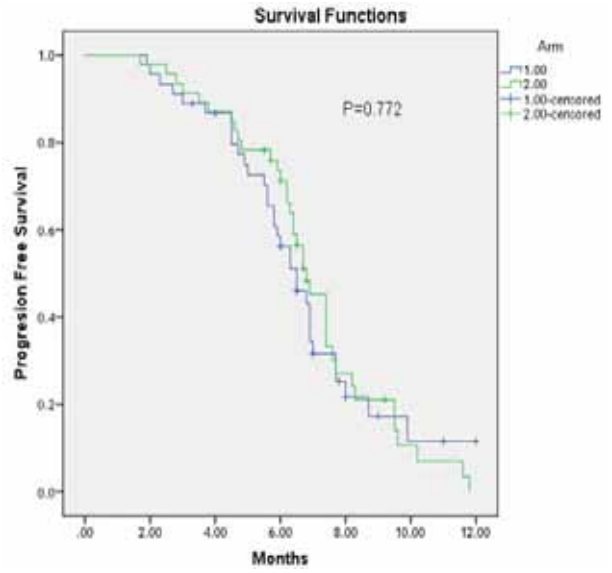


**Figure 1:** Progression-free survival (PFS) of patients with stage III& IV advanced non-small cell lung cancer treated by gemcitabine-cisplatin (arm 1, 45 patients) PFS= 6.8 months and the other arm treated by gemcitabine-docetaxel (arm 2, 46 patients) PFS= 6.5 months (log-rank *P*= 0.772).

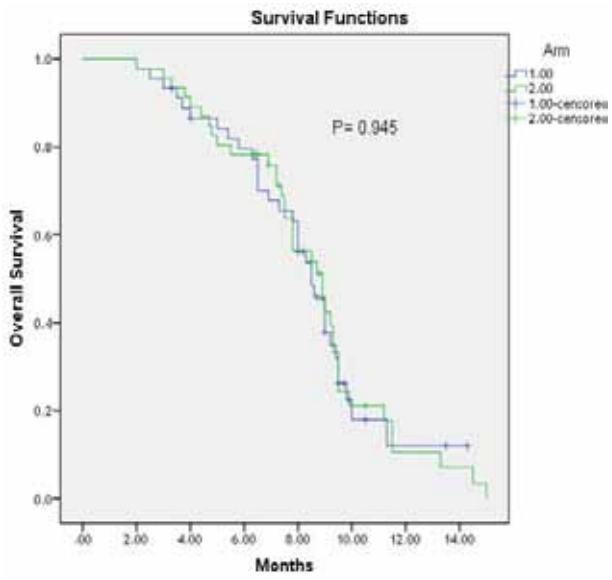


**Figure 2:** Overall survival (OS) of patients with stage III& IV advanced non-small cell lung cancer treated by gemcitabine-cisplatin (arm 1, 45 patients) median OS was 8.9 months and the other arm treated by gemcitabine-docetaxel (arm 2, 46 patients), median OS was 8.5 months (log-rank *P*= 0.945).

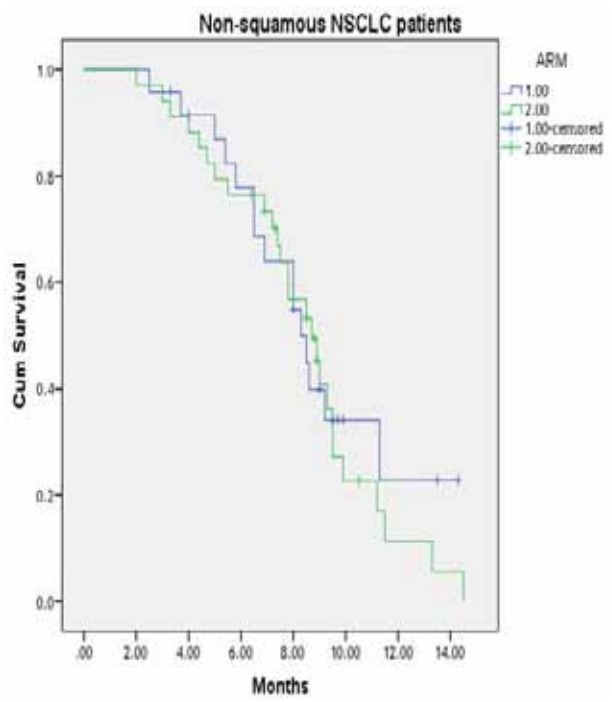


**Figure 3-A.** Overall survival of patients with non-squamous histology in arm 1(No=28) treated by gemcitabine-cisplatin and arm 2 (No=31) treated by gemcitabine-docetaxel, *P*= 0.922.

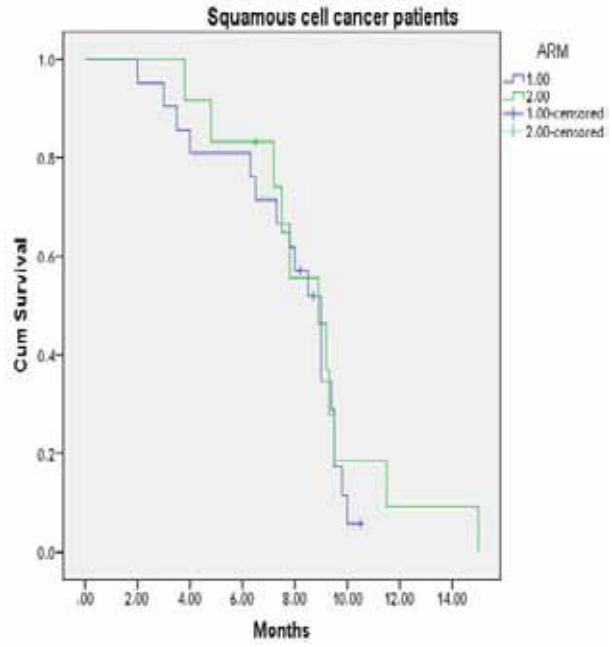


Figure 3-B. Overall survival of patients with squamous histology in arm 1 (No=17) treated by gemcitabine-cisplatin and arm 2 (No=15) treated by gemcitabine-docetaxel, *P*=0.92.

**Table 1:** Patient demographics and clinical characteristics.

| Item | Arm 1 (GC patients= 45) No.(%) | Arm 2 (GD patients=46) No.(%) | ***P*-value** |
|---|---|---|---|
| **Age "years"** | | | |
| Median | 64 | 60 | 0.780 |
| (min-max) | (37.0-73.0) | (42.0-74.0) | |
| **Sex:** | | | |
| Female | 14(31.1%) | 15(32.6%) | 0.529 |
| Male | 31 (68.9%) | 31(67.4%) | |
| **Smoking:** | | | |
| Non-smokers | 18(40%) | 16(34.8%) | 0.425 |
| Smokers | 27(60%) | 30(65.2%) | |
| **ECOG PS:** | | | |
| 0 | 18(40.0%) | 16 (34.8%) | |
| 1 | 17(37.8%) | 20 (43.5%) | 0.705 |
| 2 | 10 (22.2%) | 10 (21.7%) | |
| **Stage:** | | | |
| III | 10 (22.2%) | 7 (15.2%) | 0.279 |
| IV | 35 (77.8%) | 39 (84.8%) | |
| **metastatic sites:** | | | |
| Lymph nodes | 27 (60%) | 30 (65.2%) | |
| Other lung and pleura | 35 (77.8%) | 32 (69.6%) | |
| Liver | 10 (22.2%) | 10 (21.7%) | N.s.* |
| Bones | 17(37.8%) | 20 (43.5%) | |
| Adrenal glands | 5 (11.1%) | 7 (15.2%) | |
| **Histology:** | | | |
| Adenocarcinoma | 24(53.3%) | 25(54.3%) | |
| Squamous cell carcinoma | 17 (37.8%) | 15(32.6%) | 0.087 |
| Large Cell carcinoma | 3 (6.7%) | 6 (13.0%) | |
| Undifferentiated | 1 (2.2%) | | |
| **Histological Grade:** | | | |
| II | 35 (77.8%) | 32(69.6%) | 0.258 |
| III | 10 (22.2%) | 14 (30.46%) | |

ECOG PS = Eastern Cooperative Oncology Group (ECOG) performance status
GC= gemcitabine-cisplatin, GD= gemcitabine-docetaxel
N.s.*= no significant differences between metastatic sites distribution in the two groups

**Table 2:** Outcome of both arms.

| **Item** | **Arm 1 (GC patients= 45)** | **Arm 2 (GD patients=46)** | ***P*-value** |
|---|---|---|---|
| **Response: No. (%)** | | | |
| Partial response | 21 (46.7%) | 20 (43.5%) | |
| Stable disease | 11 (26.7%) | 12 (26.1%) | 0.489 |
| Progressive disease | 13 (28.9%) | 14 (30.4%) | |
| **Progression-free survival** | | | |
| Median (months) | 6.8 | 6.5 | 0.772* |
| S.D (min-max) | 0.302(6.208 7.392–) | 0.472(5.575– 7.425) | |
| **Overall survival** | | | |
| Median (months) | 8.9 | 8.5 | 0.945* |
| S.D (min-max) | 0.674 (7.580-10.220 ) | 0.421(7.647 – 9.326) | |

GC= gemcitabine-cisplatin, GD= gemcitabine-docetaxel, SD= standard deviation
*Log-rank test

**Table 3:** NCI-CTC grades 3/4 Toxicity of both Arms.

| Item | Arm 1 (GC patients= 45) No.(%) | Arm 2 (GD patients=46) No.(%) | *P* value |
|---|---|---|---|
| **Hematological:** | | | |
| Anaemia | 8 (17.8) | 4(8.7) | |
| Neutropenia | 19(42) | 11(24) | 0.077 |
| Thrombocytopenia | 14(31) | 7(15.2) | 0.086 |
| Febrile neutropenia | 5(11) | 3(6.5) | |
| **Non-hematological:** | | | |
| Neurotoxicity | 2(4.4) | 4(8.7) | |
| Hepatotoxicity | 4(8.8) | 3(6.5) | |
| Fatigue | 5(11) | 6(13) | |
| Mucositis | 4(8.8) | 3(6.5) | |
| Nausea & Vomiting | 8 (17.6) | 5(10.9) | |
| diarrhea | 3(6.7) | 2(4.3) | |
| renal | 1(2.2) | -- | -- |

NCI-CTC= National Cancer Institute Common Toxicity Criteria version 2.0
GC= gemcitabine-cisplatin, GD= gemcitabin-docetaxel

## DISCUSSION

The aim of the study was to compare the gemcitabine-docetaxel combination with cisplatin-gemcitabine regimen in patients with advanced or metastatic NSCLC in a phase III study.

There were no statistically significant differences in PFS and median OS between GD group and GC group (6.5 versus 6.8 months, [*P* = 0.772] and 8.5 versus 8.9 months, [*P* = 0.945] respectively). The response rates were also comparable; 46.7% for GC Arm versus 43.5% for GD Arm, (*P*=0.489). In accordance with our results, a meta-analysis comparing the efficacy and toxicity of gemcitabine plus docetaxel (GD) with platinum-based doublet in patients with untreated advanced NSCLC, found that the efficacy was comparable between both regimens according to overall survival and 1-year survival. Although platinum-based regimen had an advantage in time to progression (TTP) and overall response rate (ORR), the advantage was lost when the two trials used sequential regimens were removed[11].

In 2001, Georgoulias *et al*.[12] performed a randomized multicentre trial to compare gemcitabine plus docetaxel with platinum-based doublet. They reported that DC (Docetaxel 100mg/m$^2$, day 1, Cisplatin 80 mg/m$^2$, day 1) versus DG (Docetaxel 100 mg/m$^2$, day 8; Gemcitabine 1100 mg/m$^2$, days 1 and 8) had similar efficacy (response rate, 32.4% vs 30.2%) and survival data (median OS 10 vs 9.5 months).

Georgoulias *et al.*[13] also conducted another randomized phase III trial (413 patients) comparing Docetaxel plus Gemcitabine with Cisplatin plus Vinorelbine (VC) with prophylactic G-CSF support. Overall response rates were 30% and 39.2% (*P* = 0.053) for the DG and VC arms, respectively. Median survival time was 9.0 and 9.7 months (*P* = 0.965) for the DG and VC arms, respectively. Pujol *et al*.[14] also demonstrated that a non–cisplatin-based regimen was as effective as a cisplatin-based regimen. Their randomized phase III study compared the efficacy and safety of DG regimen (Docetaxel 85 mg/m$^2$, day 8 plus Gemcitabine 1000 mg/m$^2$, days 1 and 8) versus VC regimen (Vinorelbine 30 mg/m$^2$, days 1, 8, and 15 plus Cisplatin 100 mg/m$^2$, day 1). A total of 311 patients were enrolled. Objective response rates did not differ significantly (31% for DG, 35.9% for VC). Neither PFS nor overall survival differed significantly between the two arms (median PFS 4.2 and 4 months; median survival 11.1 and 9.6 months for DG and VC, respectively).

After that, seven other studies have evaluated the combination of Docetaxel and Gemcitabine in phase II trials. In their study of 133 patients, Katakami *et al.*[15] reported that DG (docetaxel 60 mg/m$^2$, day 8 + gemcitabine 800 mg/m$^2$, days 1 and 8, every 3 weeks) versus DC (docetaxel 60 mg/m$^2$, day 1 + cisplatin 80 mg/m$^2$, day 1, every 3 weeks) had similar efficacy (response rate, 27% vs 23.5%) and survival data (median survival time, 13.7 months versus 11.4 months). In their study, 32.4% of patients in DC arm and 30.2% of patients in DG arm received gefitinib and this may explain the apparently better overall survival. Binder *et al.*[16] tested gemcitabine (900 mg/m$^2$) on days 1 and 8, plus docetaxel (75 mg/m$^2$) on day 1 every 3 weeks versus gemcitabine (900 mg/m$^2$, days 1 and 8) and cisplatin (70 mg/m$^2$ day 1) for 3 cycles, followed by 3 cycles of docetaxel (100 mg/m$^2$, day 1 every 3 weeks). ORR , TTP, and OS

were 20.4%, 3.6 months, 8.7 months respectively in DG arm versus 31.0%, 5.2 months, 9.4 months, respectively in arm Cis-Gem+Doc ($P$>0.05). Similarly, the other five phase II trials[17-21] reported no statistical difference in survival between the two regimens.

With the exception of the better OS (13.7 months) reported by Katakami *et al*.[15], the median OS (8.5 months) of our patients is comparable to that reported in previous studies. However, the variance between the observed response rate (43%) in our study and other studies[12-21] can be attributed to using different GD regimens and small sample sizes.

Regarding toxicity, the aforementioned meta-analysis showed that GD induced less grade 3–4 nausea/vomiting, anemia, neutropenia and febrile neutropenia. Grade 3–4 diarrhea, sensory neuropathy, fatigue and thrombocytopenia were comparable between the two groups[11]. Another meta-analysis to compare platinum-based with non-platinum-based chemotherapy in advanced non-small cell lung cancer reported similar results in favor of the non-platinum doublets[22]. These results are consistent with our findings reporting that GD was associated with a more favorable toxicity profile. Grade 3/4 anemia, leucopenia, neutropenia and thrombocytopenia were worse in the cisplatin-gemcitabine group. Consequently, the incidence of febrile neutropenia was also higher with GC than with GD. Moreover, the incidence of cisplatin-related toxicities such as nausea and vomiting and nephrotoxicity were observed mainly with GC. On the other hand, grade 3 neurotoxicity was more frequent in GD arm as expected, due to the use of docetaxel. All these differences do not reach statistical significance due to small sample size.

There was also no difference in OS between the two treatment arms with regards the primary stratification factor of histology. Patients with non-squamous histology have similar OS after treatment with GD compared with GC. Previous studies have reported improved activity of platinum-based therapies in patients with adenocarcinoma compared with those with squamous tumor histology[23,24]. Further prospective studies evaluating the efficacy of docetaxel combinations in conjunction with molecular and genomic tumor analysis may be warranted.

In conclusion, the results presented in this study suggest that gemcitabine-docetaxel (GD) combination is equally active to standard cisplatin-gemcitabine (GC) regimen when used as first-line therapy in the treatment of patients with stage IIIB/IV NSCLC. The more favorable toxicity profile of GD supports its use as first-line chemotherapy, especially in patients who cannot tolerate cisplatin. However, the higher cost of the GD regimen is an issue that should be taken into account for the final therapeutic decision.

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