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A Randomized Phase II Study Comparing Two Schedules of the 21-Day Regimen of Gemcitabine and Carboplatin in Advanced Non-Small Cell Lung Cancer

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Key Words
Carboplatin · Gemcitabine · Non-small cell lung cancer · Chemotherapy · Toxicity

Abstract
Purpose: Carboplatin area under the curve (AUC) 5 ml/min on day 1 with gemcitabine 1,250 mg/m^2 on day 1 and day 8 is a widely used regimen in advanced non-small cell lung cancer. Grade 3–4 thrombocytopenia and neutropenia are frequent. The aim of this study is to investigate whether toxicity of gemcitabine/carboplatin could be reduced by administering carboplatin on day 8 instead of day 1 without a decrease in response rate (RR). ***Methods:*** Patients received gemcitabine 1,250 mg/m^2 on days 1 and 8, carboplatin AUC 5 on day 1 (arm A) or day 8 (arm B). Drugs were administered over a 21-day cycle. Toxicity and RR were evaluated weekly and every second cycle, respectively. ***Results:*** 71 patients were enrolled into the study. We found 79% (95% CI 61–91%) grade 3–4 toxicity (neutropenia and thrombocytopenia) in arm A and 50% (95% CI 32–68%) in arm B; 66% grade 3–4 thrombocytopenia in arm A and 26% in arm B. We observed 30% grade 4 hematological toxicity in arm A and 3% in arm B. In arm A an overall RR of 20% (95% CI 7.7–38.6%) was seen, and 18.2% (95% CI 7–35.5%) in arm B. ***Conclusions:*** Although the study was prematurely closed, the current data are of interest. The schedule with carboplatin on day 8 is associated with substantially lower grade 3–4 neutropenia and thrombocytopenia with comparable dose intensity and RR.

Introduction

Lung cancer is the leading cause of cancer-related deaths in many countries. Approximately one third of patients with non-small cell lung cancer (NSCLC) have metastatic disease at the time of diagnosis. Platinum-based chemotherapy remains the standard chemotherapy regimen in metastatic NSCLC [1]. Although recent meta-analyses showed a marginal statistical superiority of a combination of cisplatin with third-generation drugs [2, 3], many clinicians feel that this improvement is largely counterbalanced by the increased toxicity of the cisplatin regimen. As a consequence, the carboplatin-gemcitabine regimen is frequently used in Europe as it results

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in less severe neurotoxicity, nephrotoxicity, nausea and vomiting.

Dose-limiting toxicity in the gemcitabine/carboplatin chemotherapy regimen is hematological [4, 5]. In the 3-weekly regimen in which gemcitabine and carboplatin are administered on day 1 and gemcitabine again on day 8, thrombocytopenia grade 3–4 was found in more than 40% of cases, neutropenia grade 3–4 in 20% [6].

The hypothesis of the present study was that administration of carboplatin on day 8 instead of day 1 would result in less hematological toxicity without compromising the activity of the combination.

Methods

Patient Selection

Patients with histologically or cytologically proven stage IV or IIIB NSCLC with malignant pleural effusion or supraclavicular lymph nodes were eligible. Other criteria were measurable disease according to RECIST [7], age ≥18 years, WHO <2, and adequate bone marrow reserve. No prior chemotherapy for NSCLC was allowed. The study was approved by the ethical committee of the Erasmus MC and all participating hospitals. Patients were included after obtaining their written informed consent.

Treatment Plan

Patients in arm A were treated with gemcitabine (1,250 mg/m^2 days 1, 8) and carboplatin (area under the curve, AUC, 5 ml/min day 1). Patients in arm B were treated with gemcitabine (1,250 mg/m^2 days 1, 8) and carboplatin (AUC 5 ml/min day 8). Both drugs were administered as a 21-day cycle. Treatment was given for a maximum of 4 courses. Tumor response was assessed every second cycle. The dose of gemcitabine was reduced to 1,000 mg/m^2 and the carboplatin dose to AUC 4 if the nadir of the absolute neutrophil count (ANC) was $<0.5 \times 10^9$/l and/or the nadir of the platelets was $<50 \times 10^9$/l or in case of febrile neutropenia or severe bleeding (grade 4). If on day 21 the white blood count (WBC) was $<3 \times 10^9$/l, ANC $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l, treatment was delayed. In case the platelets were $\leq 50 \times 10^9$/l and/or the WBC $\leq 1 \times 10^9$/l and/or the ANC $\leq 0.5 \times 10^9$/l on day 8, no carboplatin or gemcitabine was given. In all other cases no dose reduction for carboplatin on day 8 was allowed.

Efficacy and Tolerability Assessments

Study assessments included physical examination, complete blood count, electrocardiogram, chest-upper abdomen computed tomography scan (CT), bone scan or PET-scan. Routine blood tests were performed before each chemotherapy administration. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2 (NCI-CTC) and assessed on days 1, 8, 15 and 21 of each cycle.

Study Design, Statistical Considerations and Analysis

The study was an open multicenter randomized phase II trial. All participants were stratified by institution, disease stage, WHO performance status, gender and age. A Bryant and Day design was used to simultaneously assess response rate and hematological toxicity as co-primary endpoints [8]. Secondary endpoints were overall survival and 1-year survival.

Based on predefined expectations that arm A (carbo/gem day 1) is associated with a grade 3–4 toxicity (thrombocytopenia and neutropenia) in 30% of cases with a response rate of 45% and that arm B (carbo/gem day 8) is associated with 15% grade 3–4 toxicity and a response rate of 45%, we designed the study as follows. Considering $P_0 = 30\%$ (unacceptable response rate) and $P_1 = 50\%$ (acceptable response rate), and $T_0 = 30\%$ (unacceptable toxicity rate) and $T_1 = 15\%$ (acceptable toxicity rate), with an alpha of 0.10 and a power of 90%, the sample size was estimated to be 67 patients in each arm. A first-stage analysis was planned for 54 patients. The following rule was applied for both arms: if 8 or less patients showed a response and/or 8 or more patients developed grade 3–4 thrombocytopenia and/or neutropenia, closure of the arm was necessary. Patients who did not receive any treatment were excluded from the toxicity analysis and patients for whom response was not assessed due to early death or early discontinuation were excluded from the activity analysis.

Response and toxicity rates, including 95% CIs, were compared using a Pearson's χ^2 test. Survival was estimated according to Kaplan Meier.

Results

Patients and Disease Characteristics

A total of 71 patients were enrolled between April 2004 and March 2006, before the planned first stage analysis. 71 patients were included instead of 54 because not all patients were evaluable for response and results of the first stage analysis were not immediately available.

Patient and disease characteristics at baseline for the 69 eligible patients are summarized in table 1.

Dose Administration and Intensity

Median dose intensity for gemcitabine in arm A was 708 mg/m^2/week (range 189–847) and in arm B 804 mg/m^2/week (range 314–849). Relative dose intensity was 85% in arm A and 96% in arm B. The median total carboplatin dose in arm A was 1,830 mg versus 2,090 mg in arm B. Gemcitabine day 1 dose reductions occurred in 9% of cycles in arm A and in 3% in arm B. For gemcitabine day 8, dose adjustments occurred in 11% of cycles in arm A and in 5% in arm B. Carboplatin doses were reduced in 9% of cycles in arm A and in only 1% in arm B.

Toxicity

The frequency of toxicity check was weekly with 7% missing values for ANC and/or platelets in arm A compared to 6% in arm B.

Table 2 shows grade 3–4 toxicity (neutropenia and thrombocytopenia) of 79% (95% CI 61–91%) in arm A

and 50% (95% CI 32–68%) in arm B. Grade 3–4 thrombocytopenia occurred in 66% of patients in arm A and in 26% in arm B. Platelet transfusions were required in 14% of patients in arm A and in 0% in arm B.

Response and Outcome

Five of 69 patients were considered unassessable for response evaluation as they did not receive at least 2 cycles of therapy. In the remaining 64 patients, we observed 1 complete response and 11 partial responses; 40 patients remained stable and 12 progressed under treatment, either radiologically and/or clinically.

In arm A, an overall response rate of 20% (95% CI 7.7–38.6%) was seen compared with 18.2% (95% CI 7–35.5%) in arm B. The median survival time for all patients was 7.3 months, with a 1-year survival rate of 28%. Median survival was 9.4 months for arm A and 6.8 months for arm B.

Table 1. Patient and disease characteristics

	Overall	Arm A	Arm B
Number of patients	69	34	35
Gender			
Male	52 (75)	25	27
Female	17 (25)	9	8
Age, years			
Median	61	61	61
Range	39–77	41–77	39–74
ECOG performance			
0	11 (16)	6	5
1	58 (84)	28	30
Stage of disease			
IIIB	13 (19)	6	7
IV	56 (81)	28	28
Histology			
Squamous	14 (20)	8	6
Adenocarcinoma	33 (48)	17	16
Other	22 (32)	9	13

Numbers in parentheses are percentages.

Discussion

With carboplatin-gemcitabine being widely used as the standard regimen in advanced NSCLC, we wanted to investigate whether the administration of carboplatin on day 8 instead of day 1 could reduce hematological toxicity without loss of activity. Based on the early stopping rule, the study was closed prematurely as response rates in both arms were lower and toxicities higher than expected. Compared to other trials, grade 3–4 hematological toxicity in the present study was high. This probably reflects the weekly sampling instead of sampling at retreatment or at clinical toxicities only. Another reason for the premature closure could be that the cut-off value for acceptable/unacceptable response and toxicity in the standard arm was too optimistic. Survival in arm B is lower than reported in the literature, but also survival in the standard arm is low. This is probably due to a high percentage of patients (81%) with stage IV disease. A limitation of the study is that the sample size is too small to reasonably consider any comparisons between the two arms in terms of survival, although survival in arm B seems lower compared to the standard arm.

Table 2. Hematological toxicities and response

Toxicity	Arm A (n = 33)	Arm B (n = 34)
Platelets/ANC grade 3–4	26 (79)	17 (50)
Platelets/ANC grade 4	10 (30)	1 (3)
Platelets grade 3–4	22 (67)	9 (26)
ANC grade 3–4	18 (55)	12 (35)
ANC grade 4	10 (30)	1 (3)
Platelets grade 4	1 (3)	0 (0)
Response		
CR	0	1
PR	6	5
SD	21	19
PD	3	9
Overall RR, %	20	18

Percent values are shown in parentheses.
CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease.

The study did not meet its primary endpoint, but the data are of interest. Response rates were found to be similar but we observed a considerably lower rate of hematological toxicity by administering carboplatin on day 8 with preservation of dose intensity.

Although a combination of cisplatin with third-generation drugs shows a marginal statistical superiority, many clinicians prefer the carboplatin-based regimens because of the better tolerance and the difficult logistics of cisplatin administration. Gemcitabine/carboplatin is frequently used in Europe for patients with advanced NSCLC [9, 10]. This regimen is well tolerated, but clinicians frequently have to deal with grade 3–4 neutropenia and

grade 3–4 thrombocytopenia. Even though severe bleeding problems are not seen very often, physicians feel uncomfortable about thrombocytopenia because it necessitates more attention, repeated platelet count controls, dose reductions and platelet transfusions [11]. The Norwegian Lung Cancer Study Group recently also reported on a grade 3 thrombocytopenia of 25% and grade 4 thrombocytopenia of 19% in the carboplatin day 1-gemcitabine regimen, resulting in more frequent platelet transfusions and higher costs [12]. Reducing hematological toxicity is important especially in patients with metastatic disease, in whom quality of life is still a major goal.

Conclusion

Although the study was stopped prematurely, we believe that the current data are of interest. With comparable dose intensity and response rate, the schedule with carboplatin on day 8 is associated with a substantially lower rate of grade 3–4 neutropenia and thrombocytopenia. The observed possibly lower median survival trend merits further investigation.

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