Gemcitabine versus Gemcitabine–Carboplatin for Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2: A Prospective Randomized Phase II Study of the Hellenic Cooperative Oncology Group

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Background: The purpose of this study was to evaluate gemcitabine–carboplatin (GCb) versus single-agent gemcitabine (G) in patients with advanced non-small cell lung cancer (NSCLC) and a performance status (PS) of 2. The primary endpoint was clinical benefit.

Patients and Methods: Patients were randomly assigned to either 1250 mg/m^2 of G (arm A) or 1250 mg/m^2 of G plus carboplatin area under the curve of 3 (arm B). Both treatments were given on days 1 and 14 and were repeated every 28 days for up to four cycles.

Results: Among the 90 eligible patients (47 in arm A and 43 in arm B), in arm A, two (4%) had partial responses (95% CI, 0.52%–14.5%) and 10 (21%) had stable disease (95% CI, 10.7%–35.7%). In arm B, six (14%) had partial responses (95% CI, 5.3%–27.9%) and nine (21%) had stable disease (95% CI, 10%–36%) ($p = 0.14$). No significant difference was found in terms of clinical benefit between the two treatment groups after two cycles of treatment or at the end of chemotherapy. Furthermore, no association was found between clinical benefit and response to treatment ($p > 0.05$). Median survival was 4.8 months (95% CI, 2.45–7.25) for arm A and 6.7 months (95% CI, 2.47–10.8) for arm B ($p = 0.49$). Neutropenia ($p = 0.007$) and thrombocytopenia ($p < 0.001$) were more common in group B. Nevertheless, no significant differences were found in terms of severe toxicities ($p > 0.05$ in all cases).

Conclusion: No significant difference was found in terms of clinical benefit in patients with NSCLC and PS 2 who received single-agent G or GCb. Nevertheless, GCb caused more toxicity, particularly neutropenia and thrombocytopenia.

Key Words: Chemotherapy, Clinical benefit, Non-small cell lung cancer, Performance status of 2, Gemcitabine, Carboplatin.

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The management of patients with advanced non-small cell lung cancer (NSCLC) has improved during the last decade. Compared with best supportive care, chemotherapy offers improvement in overall survival and substantial palliation,[1–3] and a meta-analysis has shown that cisplatin-based chemotherapy can prolong median survival by 1.5 months and 1-year survival by 10%.[4] This was improved further with the addition of newer agents that was restricted to patients with good performance status (PS).[5–8]

In several studies, a PS of 2 was proven to be the most important negative prognostic factor.[8–13]

In the Eastern Cooperative Oncology Group (ECOG) 1594 and other trials, the final analysis proved that the toxicity rate in patients with PS 2 did not differ significantly from the PS 0 and 1 cohorts.[12–14]

As single agents, vinorelbine and gemcitabine (G) were proven superior to best supportive care in median survival and quality of life.[15,16] Nevertheless, trials comparing single-agent versus combination chemotherapy offered conflicting results.[17–19]

Single-agent G has been used in elderly patients and those with poor PS.[15–17] The good toxicity profile and positive survival and quality-of-life results were the main reasons our group used G as the control arm. Carboplatin (Cb) is an accepted alternative to cisplatin, especially in patients who cannot tolerate toxicity. We elected to use G with Cb (GCb) as the experimental arm because of its good toxicity profile, its known efficacy from trials with PS 0 and PS 1, and its ease of administration through an outpatient setting.[20] The schedule and the doses of the given drugs were chosen to

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keep toxicity at the lowest level for this group of patients with poor PS.

The primary endpoint of this study was clinical benefit, which evaluated pain, cough, dyspnea, anorexia, hemoptysis, fatigue, weight loss, and general feeling. Secondary endpoints were response, survival, time to disease progression (TTP), and toxicity.

PATIENTS AND METHODS

Eligibility Criteria

Chemonaïve patients were required to be at least 18 years of age with histologically confirmed, inoperable, recurrent, or metastatic stage IIIb NSCLC with pleural effusion or stage IV NSCLC (American Joint Committee on Cancer criteria[21]). An ECOG PS of 2 was required. Prior radiotherapy was allowed. Patients were required to have completed radiotherapy at least 4 weeks before chemotherapy and to have a life expectancy of at least 12 weeks. Other requirements included measurable or assessable disease in nonirradiated fields, unless subsequent disease was documented. Patients with stable brain metastases were eligible. In addition, patients must have had adequate bone marrow reserve, kidney, and liver functions.

Patients with active infection or a history of other neoplasms (except for basal cell carcinoma of the skin or in situ carcinoma of the cervix) were excluded from the study. Patients with active cardiac disease or preexisting grade 3 or 4 motor or sensory neuropathy (World Health Organization [WHO] criteria[22]) were also excluded. Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki and the Hellenic Cooperative Oncology Group institutional policies. All patients provided informed consent before receiving study treatment.

Treatment Plan

Eligible patients were randomly assigned to either arm A or arm B. Arm A received 1250 mg/m^2 of G via 30-minute infusion with normal saline on days 1 and 14. Group B received the same G regimen plus Cb area under the curve of 3 (Calvert formula) as a 1-hour infusion on days 1 and 14. In both arms, the treatment was repeated every 28 days for two cycles; if patients had partial response, stable disease, or clinical benefit, they received two more cycles. Reasons for early discontinuation of treatment were progressive disease, intolerable or unacceptable toxicity, and volunteer withdrawal from the study. All patients received ondansentron as an antiemetic.

If patients had hematologic toxicity (platelets $<$100,000/mm^3 and neutrophils $<$1500/mm^3) or nonhematologic toxicity grade 3/4 on the day of chemotherapy, their treatment was postponed until recovery. If a delay was more than 15 days, the patient was taken off the study. If patients had grade 3 or 4 toxicity, their doses were reduced by 25% for subsequent cycles. If, after the first dose reduction, the grade 3 or 4 toxicity persisted, then the patient was taken off the study.

Treatment Evaluation

All eligible patients who received at least two cycles of chemotherapy were evaluated for efficacy. Using the intent-to-treat principle, response was evaluated according to standard WHO criteria.[22] All eligible patients who received at least one cycle of chemotherapy were evaluable for toxicity. Toxicity was evaluated according to WHO criteria.[22]

Evaluation of Clinical Benefit

The primary endpoint of this study was clinical benefit, which was based on three measures. The first measure was the Lung Cancer Symptom Scale, which consists of six symptoms: dyspnea, cough, hemoptysis, fatigue, anorexia, and pain; these symptoms were scored on a visual analogue scale ranging from 0 to 100.[23,24] The second measure was of general feeling (very good, good, or poor), which was also scored on a visual analogue scale ranging from 0 to 100. The third measure was the patient's weight (in light dress, without shoes, and using a consistent scale).[25–27] Along with the analogue scale, patients reported improvement or worsening for each scale item.

After randomization, patients were weighed and recorded their symptoms and general feeling on a special diary card. After cycle 2, patients completed the visual analogue scale of symptoms and general feeling, expressing the positive or negative changes during the last 4 weeks in comparison with their baseline assessment. Their weight was also recorded at this time. Similar procedures took place 2 weeks after cycle 4, which was the end of treatment. In any case, all new symptoms were recorded in the patient's diary card.

Statistical Analysis

The sample size was calculated on the assumption that a 0.6 standardized difference in clinical benefit existed between the two arms. For an alpha error of 0.05 and power of 80%, each arm needed to enroll 45 patients. The total number of patients was estimated at 92, taking into consideration a 3% withdrawal rate. An interim analysis was not planned.

Overall survival was measured from the day of randomization until death from any cause. Surviving patients were censored on the day of the last contact. TTP was measured from the day of randomization until the date progression of the disease was first documented.

Chi-square and Fisher's exact tests were used to compare major patient and tumor characteristics, symptoms before chemotherapy, and clinical benefit data between the two arms. The Kaplan–Meier method was used to calculate overall survival and TTP curves, and the log-rank test was used to compare time with event distributions.[28] All of the analysis was performed using SPSS system software, and in all cases a p value of <0.05 (two tailed) was considered significant.

RESULTS

Baseline Patient Characteristics

From October 2000 to March 2003, 102 patients entered this study. Two patients with incomplete medical records were excluded from the analysis. Ten patients were considered ineligible. Seven patients were inadvertently ran-

TABLE 1. Baseline Patient and Tumor Characteristics

	Gemcitabine (Arm A, $n = 47$)	Gemcitabine–Carboplatin (Arm B, $n = 43$)
Age (yr)		
Median	73	70.5
Range	48–87	51–88
Gender, *n* (%)		
Male	39 (83)	31 (72)
Female	8 (17)	12 (28)
Stage, *n* (%)		
IIIb–IIIb wet	17 (36)	11 (26)
IV	30 (64)	32 (74)
Prior radiotherapy, *n* (%)		
Yes	11 (23)	12 (28)
No	35 (75)	30 (70)
Unknown	1 (2)	2 (2)
Histology, *n* (%)		
Squamous cell	13 (28)	13 (30)
Adenocarcinoma	27 (57)	24 (56)
Undifferentiated	4 (9)	4 (9)
Unclassified	—	1 (2)
Unknown	3 (6)	1 (2)
Metastatic sites, *n* (%)		
Lymph nodes	24 (51)	27 (63)
Pleural effusion	21 (45)	11 (26)
Liver	9 (19)	10 (23)
Bones	16 (34)	14 (33)
Brain	6 (13)	4 (9)
Adrenal glands	2 (4)	5 (12)
Number of metastatic sites, *n* (%)		
1	18 (38)	15 (35)
2	15 (32)	18 (42)
≥3	12 (26)	9 (21)
Unknown	2 (4)	1 (2)

domized (PS < 2), two received protocol treatment as second line, and one had another cancer.

Therefore, 90 eligible patients were analyzed in this study. Forty-seven were allocated to arm A (G) and 43 to arm B (GCb).

The baseline patient characteristics are presented in Table 1.

Of the 90 eligible patients, 44 patients in arm A and 39 patients in arm B were included in the baseline clinical benefit analysis. The baseline clinical benefit parameters of weight loss and general feeling were well balanced between arms ($p > 0.05$ in all cases) (Table 2).

Response

In both arms, all patients were evaluable for efficacy. In arm A, two patients (4%) had partial response (95% CI, 0.52%–14.5%) and 10 patients (21%) had stable disease (95% CI, 10.7%–35.7%). In arm B, six patients (14%) had partial response (95% CI, 5.3%–27.9%) and nine patients (21%) had stable disease (95% CI, 10%–36%). There was no statistical significance between the two arms ($p = 0.14$).

TABLE 2. Baseline Clinical Benefit Assessments

	Gemcitabine (Arm A, $n = 44$)	Gemcitabine–Carboplatin (Arm B, $n = 39$)
Assessment, *n* (%)		
General feeling		
Very good/good	19 (43)	19 (49)
Poor	25 (57)	20 (51)
Pain	17 (39)	18 (46)
Cough	22 (50)	20 (51)
Fatigue	27 (61)	23 (59)
Dyspnea	21 (48)	15 (38)
Anorexia	17 (39)	17 (44)
Hemoptysis	0	0
Weight loss	19 (43)	16 (41)

Clinical Benefit Analysis

The main comparison regarding clinical benefit is based on the general feeling parameter. The Lung Cancer Symptom Scale parameters, because of the high rate of missing values, are presented here mainly for descriptive purposes. Only percent improvement by cycle is presented here, because of the high missing value rate on the visual analogue scale for the clinical benefit parameters. The clinical benefit analysis after cycle 2 is shown in Table 3. No statistically significant difference ($p = 1.0$) was found between the two arms in terms of general feeling after two cycles of treatment. Regarding symptoms, when compared with the baseline values, each arm had improvement in all parameters except anorexia (group A). Nevertheless, there is no significant difference between the two arms ($p > 0.05$ in all comparisons).

Twenty-three patients with partial or stable disease had general feeling estimates after two cycles of treatment. Among them, 16 (70%) reported an improvement. The respective percentage among nonresponders was 60% (18 of 30 patients) ($p = 0.57$).

Although fewer patients were assessed for clinical benefit after cycle 4, there was still some improvement in some of the symptoms (Table 3), although not significant ($p > 0.05$ in all comparisons). General feeling at the end of treatment did not differ significantly between the two arms ($p = 0.53$).

At this stage, only 38 patients had data for general feeling. Again, no association was found among those who responded to chemotherapy and those who did not (58% versus 36%, $p = 0.33$) in terms of an improvement in general feeling.

Time-to-Event Measures

After a median follow-up of 18.5 months (range, 0.1–28), 74 patients (82%) had progressed (39 in group A and 35 in group B) and 72 (80%) had died (39 in group A and 33 in group B). The median survival was 4.8 months (range, 0.1–18.8; 95% CI, 2.45–7.25) in group A and 6.7 months (range, 0.1–28+; 95% CI, 2.47–10.8) in group B ($p = 0.49$) (Figure 1). Furthermore, median TTP was 2.98 months (range, 0.01–18.7; 95% CI, 2.26–3.71) in group A and 4.07 months (range, 0.01–28; 95% CI, 2.23–5.9) in group B ($p =$

TABLE 3. Clinical Benefit Analysis

	Gemcitabine (Arm A)			Gemcitabine–Carboplatin (Arm B)			
	n	*n* Improved	%	*n*	*n* Improved	%	*p*
Clinical benefit after cycle 2							
General feeling	28	18	64	26	17	65	1.0
Pain	15	10	67	17	9	53	0.49
Cough	18	11	61	17	10	59	1.0
Fatigue	20	11	55	18	11	61	0.75
Dyspnea	16	10	63	11	6	55	0.7
Anorexia	13	6	46	18	11	61	0.48
Weight loss	14	10	71	14	9	64	1.0
Clinical benefit after cycle 4							
General feeling	21	11	52	17	7	41	0.53
Pain	7	3	43	8	4	50	1.0
Cough	13	9	69	7	5	71	1.0
Fatigue	12	7	58	8	4	50	1.0
Dyspnea	12	9	75	3	1	33	0.24
Anorexia	6	4	67	6	6	100	0.46
Weight loss	7	5	71	4	1	25	0.24

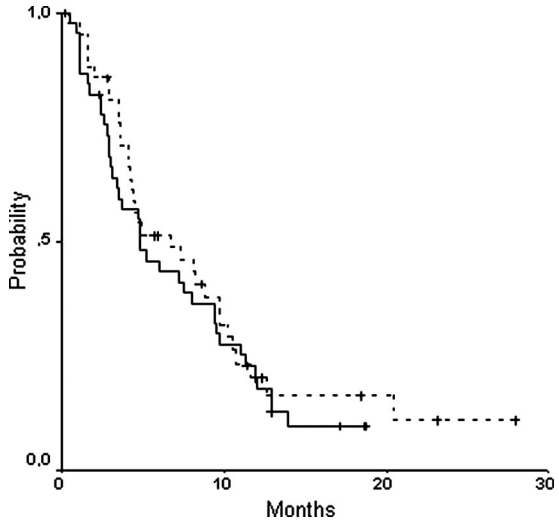

FIGURE 1. Effect of gemcitabine (*solid line*) and gemcitabine–carboplatin (*dashed line*) on overall survival

0.36). The respective 1-year survival for group A and B was 17.8% and 20%, and the probability of being without progression beyond the first year was 10.6% for group A and 14.8% for group B.

Toxicity

Two patients in group A and one in group B did not receive treatment and were thus excluded from toxicity analysis. Furthermore, two patients randomized in group B received Gemzar only.

Overall, the treatments were well tolerated by both arms. No toxic hospitalizations or deaths occurred during the treatment period. Although neutropenia was more common in group B (8.5% versus 32.5%, $p = 0.007$), severe neutropenia did not differ between the two groups (2% versus 7.5%, $p = 0.33$). Thrombocytopenia did not occur in arm A, but it occurred in 10 patients (25%) in arm B ($p < 0.001$). Severe thrombocytopenia did not differ significantly between the two treatment arms (0% versus 7.5%, $p = 0.09$). Grade 3 anemia was reported in one patient (2%) in arm A and in three patients (7.5%) in arm B, a nonsignificant difference ($p = 0.33$). There were no instances of bleeding or infection. Grade 3/4 nonhematologic toxicity was very rare in both arms, without any significant difference.

Treatment Administration

A total of 292 cycles was administered in arm A and 242 cycles in arm B. In group A, 30 (64%) patients discontinued their treatment, whereas 31 (72%) discontinued their treatment in group B. The most common cause of discontinuation was disease progression (18 patients in group A versus 14 in group B). Additional reasons for treatment discontinuation were death attributable to tumor (seven versus six), voluntary withdrawal (four versus six), doctor's decision (one versus three), and other reasons (zero versus two). One patient from group B died suddenly, after the first day of the third cycle, from a cardiovascular accident, which was possibly unrelated to treatment or disease.

Significantly more cycles in group a were given at more than 90% of the planned dose (86% versus 64%, $p < 0.001$).

DISCUSSION

Patients with advanced NSCLC and PS 2 are a unique group and have attracted the recent interest of investigators. As an independent negative prognostic factor, PS 2 was related to chemotherapy intolerability; thus, these patients were excluded from clinical research and the potential benefit

of chemotherapy in daily practice.[8–13] A 2001 analysis of the ECOG 1594 trial refuted this claim. The analysis of this trial concluded that the shorter survival time was disease related and not treatment related.[14]

The combination of G and Cb has known efficacy and good toxicity profile in patients with NSCLC and PS 0 or 1.[29] In our study, the toxicity was well tolerated in both arms, and no toxic deaths occurred. Although the incidence of grade 3/4 toxicity was low in both arms, neutropenia ($p = 0.007$) and thrombocytopenia ($p < 0.001$) were significantly worse in the GCb arm compared with the G arm. Nevertheless, the lack of serious infections and bleeding support the low toxicity profile of both regimens, especially in this group of patients in whom palliation and quality of life are the main goals. Certainly, the low dose intensity of both drugs given to this group of patients with poor PS explains the low toxicity.

Although the response rate was higher in the GCb arm (14%) in comparison with the G arm (4%), the difference was not statistically significant ($p = 0.14$). Even when the response rate was combined with stable disease (35% in the GCb arm, 25% in the G arm), the difference was not statistically significant between the two arms ($p = 0.36$). For time-to-event measures, there were no statistically significant differences in survival ($p = 0.49$), TTP ($p = 0.36$).

The comparison with other similar trials is interesting. In the MILES phase III trial,[17] the comparison vinorelbine–G was associated with more thrombocytopenia and hepatotoxicity than with single-agent vinorelbine and with more neutropenia, vomiting, fatigue, extravasation sequellae, cardiotoxicity, and constipation than with single-agent G. Measures of quality of life were similar in all arms.

In the subanalysis of the CALGB 9730 phase III trial, of 99 patients with PS 2, the median survival (4.7 versus 2.4 months) and 1-year survival (18% versus 10%) were statistically significant in favor of the combination paclitaxel–Cb.[19]

In another approach, an ECOG trial (E1599)[30] evaluated two combination regimens: 200 mg/m^2 of paclitaxel and Cb area under the curve of 6 mg/mL per minute every 3 weeks versus 1000 mg/m^2 of G on days 1 and 8 and 60 mg/m^2 of cisplatin on day 1. Disease-control rates, median survival, and TTP were similar in both arms. Thrombocytopenia was more pronounced in the cisplatin–G arm, whereas neurotoxicity was more common in the paclitaxel–Cb arm.

The clinical benefit analysis cannot substitute for quality-of-life measurement. There is a distinction between the two assessments, and clinical benefit is part of the overall quality of life of patients. It is also known that improvement of clinical benefit may have a modest impact on overall quality of life.[31] Nevertheless, in this group of patients with poor performance status, short survival, very limited social activity, low response rate, and increased progressive disease, frequent assessments are difficult, and the dropout rate is high. Also, the amount of missing data in a multiple-endpoint instrument, combined with small group of patients, may jeopardize the results. Our group considered these reasons when we elected to use the clinical benefit as the symptomatic dimension of quality of life.

In our study, the majority of patients who answered the clinical benefit questionnaire had improvements of symptoms and general feelings after cycle 2. The difference of this improvement between the two arms was not statistically significant. By the end of cycle 4, the majority of patients (52%) in arm A had continued improvements in general feelings, and a minority of patients (41%) in arm B further improved ($p = 0.53$). Nevertheless, the number of patients at that point was small, and the decreasing improvement in the arm B cannot be precisely related to disease progression or chemotherapy toxicity.

The clinical benefit for patients with NSCLC and PS 2 that has been reported in other studies is consistent with our findings.[16,26,27,32] Nevertheless, in our trial, combination chemotherapy was not proven superior to single-agent chemotherapy in terms of response, survival, or clinical benefit, and it was proven more toxic.

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