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Randomized multicentric phase II study of carboplatin/gemcitabine and cisplatin/vinorelbine in advanced non-small cell lung cancer GFPC 99-01 study (Groupe français de pneumo-cancérologie)

P. Thomas[a,*], G. Robinet[b], S. Gouva[b], P. Fournel[c], H. Léna[d], H. Le Caer[e], M. Perol[f], H. Berard[g], P. Bombaron[h], A. Vergnenegre[i], J.P. Kleisbauer[a]

[a] *Service d'Oncologie Respiratoire, Hôpital Sainte-Marguerite, 270 Bd Sainte-Marguerite, 13009 Marseille, France*
[b] *Service d'Oncologie Thoracique, Hôpital Morvan, 29200 Brest, France*
[c] *Service de Pneumologie, Hôpital Nord, Centre Hospitalier Universitaire de Saint-Etienne, 42055 Saint-Etienne Cedex, France*
[d] *Service de Pneumologie, Centre Hospitalier Universitaire de Rennes, Rue Henri Le Guilloux, 35033 Rennes Cedex, France*
[e] *Service de Pneumologie, Centre Hospitalier, Route de Montferrat, 83300 Draguignan, France*
[f] *Service de Pneumologie, Hôpital de la Croix-Rousse, 69317 Lyon Cedex 04, France*
[g] *Service de Pneumologie, Hôpital d'Instruction des Armées, 83000 Toulon, France*
[h] *Service de Pneumologie, Centre Hospitalier, BP 1370, 68070 Mulhouse Cedex, France*
[i] *Service de Pathologie Respiratoire, Hôpital du Cluzeau, 51 Avenue D. Larrey, 87042 Limoges, France*

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Summary
Purpose: To evaluate the efficacy and safety of gemcitabine and carboplatin in the treatment of previously untreated patients with advanced non-small cell lung cancer (NSCLC).
Methods: A randomized phase II study was conducted by the Groupe Français de Pneumo-Cancérologie (GFPC) in 15 centers. The patients were randomized in either arm A (GC): gemcitabine 1250 mg/m^2 on days 1 and 8 + carboplatin AUC 6 mg/(mL min) on day 1; or in arm B (VP): vinorelbine 30 mg/m^2 weekly + cisplatin 80 mg/m^2 on day 1. Treatment cycles were repeated every 3 weeks.

* Corresponding author. Present address: Service de Pneumologie, Centre Hospitalier, 1 Place Auguste Muret, 05 000 Gap, France. Tel.: +33 4 92 40 61 26; fax: +33 4 92 40 61 90.
E-mail address: pascal.thomas@ch-gap.fr (P. Thomas).

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Results: A total of 100 patients were randomized with stage IV or stage III NSCLC with malignant pleural effusion: 51 patients in arm A and 49 patients in arm B. A total of 190 cycles were administered in the GC arm and 172 cycles in the VP arm, with a median of four cycles per patient in each arm. The dose intensity was 84.9% for gemcitabine, 99.8% for carboplatin, 97.7% for cisplatin and 67.7% for vinorelbine. The objective response rates were 19.6% (95% CI, 9.8—33.1) for GC and 29.2% (95% CI, 17.0—44.1) for VP in an ITT analysis. The response duration was 169 days in arm A and 226 days in arm B.

The TTP was similar with 140 days (GC) and 148 days (VP), respectively. Overall survival rates were 334 days in the GC combination and 304 days in the VP combination. Overall, the treatment was safe and toxicities observed were different in each arm: neutropenia was the most common toxicity in the VP treatment, whereas thrombocytopenia was more frequent in the GC combination. Anemia was similar in both arms. Non-haematologic toxicity was mild. One toxic death in arm A and three toxic deaths in arm B were observed.

Conclusion: In terms of response rate, the gemcitabine—carboplatin combination was not efficient enough to allow further phase III study. Survival data are in the same range as the standard arm. This chemotherapy is feasible and may represent an alternative to a standard cisplatin-based regimen, allowing treatment in an outpatient setting.

1. Introduction

In France, the incidence of lung cancer is rising with up to 27,000 new cases per year, 80% of which are NSCLC and more than one-third are presented with metastasis at diagnosis. The best supportive care was considered as the standard treatment for advanced disease until recent overviews suggested the benefits of chemotherapy with platinum-based regimens, improving survival rate and quality of life [1,2]. Combinations including cisplatinum and mitomycin, ifosfamide [3] or vindesin [4] were the most frequent regimens used in this setting. However, chemotherapies introducing vinorelbine in combination with cisplatin were developed and have proved advantageous over a vindesin—cisplatin regimen [5]. This was then considered as a reference option and was the main treatment prescribed in many centers.

However, the efficacy and tolerability of cisplatin-based chemotherapy remains low, and combinations including new compounds have been developed with the aim of improving the treatment's efficiency and therapeutic index. Several new drugs have been proposed and have offered new opportunities for the treatment of this severe disease [6].

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite showing efficacy and safety profiles as a single agent or in combinations in NSCLC management [7]. With an objective response rate of 20% and an overall survival time of 9 months (when used as a single agent [8]) and a lack of overlapping toxicity with other cytotoxic drugs, gemcitabine is a drug easy to use in combinations. The most frequent side effects associated with gemcitabine administration are: flu-like syndrome, fever, myelotoxicity (mostly on white blood cells) and liver toxicity represented by a transient rise in liver enzymes but which is generally low to moderate.

Both, cisplatin and gemcitabine, with different mechanisms of action, play a role in the inhibition of DNA repair. The combination of both drugs has demonstrated a synergism in preclinical models and has been widely tested in phases II and III studies. The treatment usually consists of a 4-week schedule with 100 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of gemcitabine on days 1, 8 and 15. More recently, different schedules and dose administrations have been tested and the 3-week cycle with the administration of gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 is the most commonly used schedule [9,10]. In multicentric studies, this treatment allowed an objective response rate of 26—65% with a low-toxicity profile [11—14].

However, specific cisplatin toxicities like nausea and vomiting, nephrotoxicity and neurotoxicity can alter the therapeutic index. The administration of this drug needs parenteral hydration, which can complicate the treatment. For these reasons, a cisplatin analog, carboplatin was developed in order to reduce the side effects and to simplify the administration. This drug also has a direct effect on DNA, but with the toxicity profile dominated by a myelosuppression, the effect is essentially on platelets. Nephro-toxicity, neurotoxicity and digestive toxicity are reduced when compared to cisplatin.

Therefore, because of a synergistic activity on DNA and no overlapping toxicity, gemcitabine and carboplatin administration makes it possible to have treatment on an outpatient basis.

Several studies have been conducted using this combination, and no pharmacokinetic interaction has been found. Various dosages have been tested using a 4-week schedule, but with a high incidence of thrombocytopenia. A previous phase I study performed by the GFPC recommends the administration of gemcitabine 1250 mg/m^2 on days 1 and 8 and carboplatin AUC 6 on day 1, on a 3-week schedule [15]. Once the feasibility of this treatment has been demonstrated in phase I, a phase II study is recommended to define the activity and the tolerability of such a regimen in the treatment of advanced NSCLC.

The GFPC decided to test this active combination and the standard treatment represented by the vinorelbine—cisplatin [16] combination, in a randomized open phase II study. The aim of this study was to evaluate the efficacy and tolerability of this promising combination, and of the standard schedule in similar populations and study conditions. Carrying out a multicentric randomized phase II study provides enough information before starting a large phase III study.

2. Patients and methods

2.1. Eligibility criteria

Eligible patients were aged between 18 and 70 years, with a histologic or cytologic diagnosis of NSCLC, with an Eastern Cooperative Oncology Group (ECOG) score $\leq$2 and a life expectancy $\geq$12 weeks. Patients had to present a stage IV disease but without brain metastasis or stage IIIB disease with malignant pleural effusion proven by cytology. Previous radiation therapy but no previous chemotherapy was allowed. Normal hepatic and renal functions, and an adequate bone marrow reserve were required: total bilirubin $\leq$1.25 times the upper normal limit (ULN), ASAT and ALAT < 3 ULN, ALP < 2,5 ULN, and creatinine concentration $\leq$ 110 μmol/L, white blood cells $\geq 4 \times 10^9$ L^{-1} with neutrophils > 1.5×10^9 platelets $\geq 100 \times 10^9$ L^{-1}, haemoglobin $\geq$10 g/dL.

In addition, patients were required to have at least one bidimensionally measurable target lesion outside the irradiation field, $\geq$2 cm on a computerized tomographic (CT) scan. Bone metastases and pleural or peritoneal effusions were not considered as measurable lesions.

Patients were excluded from the trial for any of the following reasons: an active uncontrolled infection or fever >38.3 °C, unstable coronary cardiac disease, peripheral neurotoxicity >grade 1, psychiatric disorders, previous malignant disease (except in situ carcinoma of the cervix or adequately treated basal or squamous cell carcinoma of the skin), brain metastasis, superior cava syndrome, pregnancy or breastfeeding. Concomitant irradiation was not permitted except for palliative reasons and in a restricted field. All patients were required to provide written informed consent and the protocol was approved by the institutional ethics committee.

2.2. Study design

This study was a randomized open study. Its primary objective was to evaluate the response rate (RR) of gemcitabine—carboplatin combination in the treatment of patients with a stage IV or IIIB with malignant pleural effusion NSCLC. Secondary objectives included the evaluation of toxicities, response duration, median time to progression (TTP) and overall survival. The first end point for efficacy was the objective response in intent to treat analysis. The patients were stratified according to center and ECOG score (0 and 1 versus 2).

Patients were designed to receive either carboplatin—gemcitabine (GC) combination (arm A) or cisplatin—vinorelbine (VP) combination (arm B).

The arbitrary number of 50 patients per arm was determined. In order to reject the gemcitabine—carboplatin combination in the case of non activity, a recruitment schedule was applied according to Fleming rules [17]. With this new chemotherapy being considered as non active, with a 15% response rate and active with a 30% response rate, with an α risk of 0.12 and a β risk of 80%, the following design was applied: analysis of the first 20 patients, less than three objective responses, the study was terminated; more than seven objective responses (OR), the combination was determined as active treatment, allowing for a phase III study; between three and seven responses, allowing for recruitment of up to 15 more patients.

If after analysis of the 35 first patients, there were less than seven objective responses, the study was terminated; with nine or more objective responses, a phase III was permitted; with seven to nine objective responses, recruitment was extended to up to 50 patients.

Subsequently, with 50 patients in each arm, an objective response rate $\leq$15% was judged insufficient, and an objective response rate $\geq$22% was judged active enough to allow a phase III study.

2.3. Treatment administration

Patients randomised in arm A received carboplatin AUC 6 mg/(mL min) determined using the Calvert formula [18] after creatinine clearance evaluation with the Cockroft formula [19]. Carboplatin was administered as a 30-min infusion on day 1 of a 21-day cycle (D1—D22 and D43). Gemcitabine was administered at 1250 mg/m^2 as a 30-min infusion on days 1 (after carboplatin) and 8.

Doses were adjusted according to neutrophils, platelet count and peripheral neuropathy. On days 22 and 43, doses could be delayed for no more than 2 weeks, otherwise, the patient was withdrawn from the study. In the case of grade $\geq$3 neurotoxicity or renal toxicity, the patient was withdrawn from the study. Gemcitabine was also adjusted with regards to the hepatic function.

In arm B, patients received a 3-week schedule of cisplatin 80 mg/m^2 in a 1 h infusion on days 1, 22 and 43 with pre- and post-hydratation, and vinorelbine at 30 mg/m^2 as a 20-min infusion weekly from day 1 to day 57.

Doses of both drugs were also adjusted according to neutrophils and platelet counts. Cisplatin doses were reduced subject to vomiting, renal function and peripheral neurotoxicity. In the case of grade $\geq$3 neurotoxicity or renal toxicity, the patient was withdrawn from the study. Vinorelbine doses were adapted according to the total bilirubin.

In the case of grade $\geq$3 mucositis, cisplatin and vinorelbine, doses were reduced to 60 mg/m^2 and 25 mg/m^2, respectively.

For the comfort of the patients, all concomitant treatments were permitted, such as: antiemesis medications, antibiotics, corticosteroids, palliative irradiation. The use of granulocyte colony stimulating factors was permitted except as primary prevention on the first cycle. Whenever possible, both treatments were administered on an outpatient basis.

After tumour evaluation, either on day 63 or after three courses and in the case of stable disease or objective response, the same treatment was administered for two more cycles. A second evaluation was scheduled 2 weeks after the final administration of gemcitabine (arm A) and 1 week after the final administration of vinorelbine (arm B), that is to say on day 105 where there was no delay at all. In the case of progression, the decision for further treatment was made by the investigator. After five courses it was at the discretion of the investigator whether the same chemotherapy was to be continued or whether follow up was permitted.

Treatment had to be terminated after either unacceptable toxicity or toxicity according to protocol, progressive disease at any time or patient refusal.

2.4. Pre-treatment and follow-up evaluations

Before entering the study, the patients had a complete physical evaluation, a complete blood count, blood chemistries, an evaluation of hepatic and renal functions, an electrocardiogram plus a cardiac ultrasound in case of cardiac history. At baseline, the tumor assessments were performed using a chest X-ray, a chest, brain and adrenal gland areas CT scan, a hepatic examination by either a CT scan or an ultrasound, and a bone scan.

2.4.1. Tolerability assessment

Before each treatment administration, a complete physical examination was performed including an evaluation of any clinically accessible tumor, a toxicity assessment according to NCI criteria, complete blood count and blood chemistries.

During the study, a complete blood count was scheduled weekly.

2.4.2. Efficacy assessment

Tumor evaluation was performed after three courses in both arms, using the same evaluation technique. In the case of doses being delayed, tumor assessment had to be performed 3 weeks after the last cisplatin or carboplatin administration. Tumor assessment could have been carried out at any time if disease progression was suspected. The patients considered evaluable for response were those that were treated according to inclusion criteria and for whom an evaluation had been possible.

For partial or complete response it was necessary to have confirmation by tumor assessment, 4—8 weeks later, unless the response was downgraded to stable disease.

In the case of early treatment discontinuation for toxicity, tumor evaluation was also warranted. For patients remaining under study treatment, a second evaluation was planned 3 weeks after the fifth cisplatin or carboplatin administration.

2.4.3. Follow up evaluation

A follow up evaluation was performed every 2 months until death.

2.5. Statistical analysis

Every enrolled patient was evaluated for response to treatment, response duration, time to progression and survival time. Response was determined according to the WHO criteria. A patient was considered as evaluable if the evaluation of response was carried out. Response duration was calculated for partial responders by the interval between the first day of chemotherapy and the day of progression of the disease. In the case of complete response, the reference day is the day the response was observed. Time to progression was measured from the date of first treatment administration until the time of progressive disease or relapse. Survival time was measured from the date of first treatment administration until death, or until the date of most recent information. Duration of treatment was reported in terms of the number of cycles and number of days per cycle where the treatment was administered. All variables were analyzed in intent to treat (ITT) and per protocol (PP) populations.

Descriptive statistics were calculated and differences in patients' characteristics between arms were verified by a Chi-square test (or a Fisher exact test, if relevant) for qualitative variables and by a *t*-test for quantitative variables. The time to progression and survival rate was evaluated with a log-rank test (Kaplan—Meier method for survival analysis). All tests were two-sided and interpreted at an error risk of 5%.

The safety was assessed on all enrolled patients with haematologic and non-haematologic toxicity according to the NCI criteria (1997 version) [20].

SAS software was used for the statistical analysis.

3. Results

At the time of analysis, the median follow-up was 304 days in ITT (range: 13—1022) populations and 302 days in PP populations (range: 13—1001).

3.1. Patients' characteristics

From December 1999 to February 2002, 100 patients, (51 in arm A and 49 in arm B) were enrolled in the study, in 15 different French centers. No discrepancies between the two arms in terms of patients' characteristics were observed (see Table 1).

In terms of tumor characteristics, there were no discrepancies regarding the stage ($p = 0.21$) with a majority of stage IV disease: 86.3% in arm A and 95.9% in arm B. There were no significant histological differences ($p = 0.08$), even if adenocarcinoma was more frequent in arm A with 56.9% compared

Table 1 Patients characteristics

Patients characteristics	Arm A ($N = 51$) *n* (%)	Arm B ($N = 49$) *n* (%)	Overall ($N = 100$) *n* (%)	*p*-value comparing A and B
Sex				
Female	9 (17.6%)	8 (16.3%)	17 (17.0%)	0.86
Male	42 (82.4%)	41 (83.7%)	83 (83.0%)	
Age (years)				
Median	60.0 (44.0—69.0)	56.0 (35.0—69.0)	58.0 (35.0—69.0)	0.40
PS 0-1/PS 2				
PS 0-1	44 (86.3%)	43 (87.8%)	87 (87.0%)	0.83
PS 2	7 (13.7%)	6 (12.2%)	13 (13.0%)	
Stage 3B/4				
3B	6 (11.8%)	2 (4.1%)	8 (8.0%)	0.21
4	44 (86.3%)	47 (95.9%)	91 (91.0%)	
Histology				
Adenocarcinoma	29 (56.9%)	17 (34.7%)	46 (46.0%)	0.08
Squamous cell carcinoma	18 (35.3%)	25 (51.0%)	43 (43.0%)	
Large cell carcinoma	4 (7.8%)	7 (14.3%)	11 (11.0%)	
% Weight loss				
<5%	20 (39.2 %)	30 (61.2 %)	50 (50.0 %)	0.0454
5—10%	20 (39.2 %)	9 (18.4 %)	29 (29.0 %)	
>10%	11 (21.6 %)	10 (20.4 %)	21 (21.0 %)	

to 34.7% in arm B, and 35.3% of squamous cell carcinoma in arm A, 51% in arm B. Very few large cell carcinoma were treated.

3.2. Efficacy

The efficacy analysis included all patients enrolled, except one patient in arm B, a patient with tuberculosis discovered after inclusion and thus not treated at all. So, the ITT populations were 51 patients in arm A and 48 patients in arm B.

Evaluable patients were 48 patients in arm A (two ineligible patients: one patient with brain metastasis and one with stage I disease; one patient was not evaluated after early discontinuation for severe toxicity) and 42 patients in arm B (two ineligible patients: one without NSCLC and one with brain metastasis and four non-evaluable patients, mainly because of early discontinuation for toxicity).

Response rates calculated with an ITT analysis were 19.6% (10/51 patients, 95% CI: 9.8—33.1%) in arm A and 29.2% (14/48 patients, 95% CI: 17.0—44.1%) in arm B. Seventeen patients (33.3%) in arm A and 10 patients (20.8%) in arm B had stable disease. After per protocol analysis, response rate was 20.8% (10/48 patients, 95% CI: 10.5—35.0%) in arm A and 33.3% (14/42 patients, 95% CI: 19.6—49.5%) in arm B. No complete response was observed in any treatment arm (see Table 2). The median duration of response was 169 days (51—543) in arm A and 226.5 days (66—530) in arm B.

At the time of analysis, follow up was carried out for all patients. The latest evaluation in December 2004 showed that 10 patients were still alive. With median follow up of 304 days (range: 13—1022 days) and according to an ITT analysis, median time to progression (TTP) was 140 days (95% CI: 72—218) for arm A and 148 days (95% CI: 118—210) for arm B (see Fig. 1). Almost all patients had progressed at this time, but few patients had progressed while on study: 21/51 patients in arm A and 18/48 patients in arm B.

Table 2 Response rate—ITT population

	Arm A ($N = 51$) n (%)	Arm B ($N = 48$) n (%)
Eligible	49 (96)	46 (96)
Non-evaluable	1 (0.02)	4 (0.08)
Partial response	10 (19.6)	14 (29.2)
Progression	21 (41.1)	18 (37.5)
Stable	17 (33.3)	10 (20.8)
Overall response rate (ITT) (%)	19.6	29.2
95% CI	9.8—33.1	17.0—44.1
Duration of response (median) (days)	169	226.5

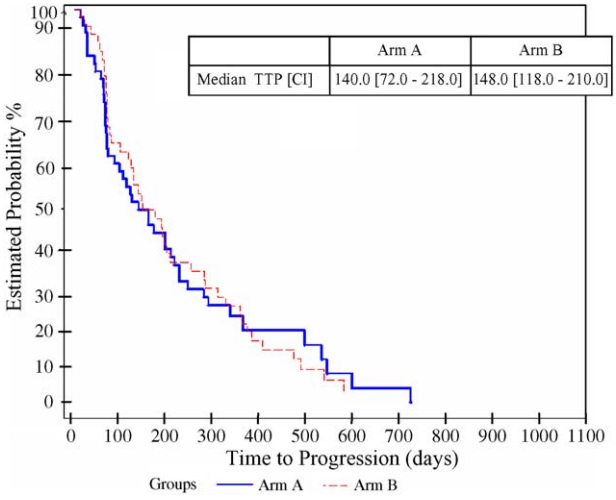

Fig. 1 Time to progression (ITT).

The median survival time for patients in arm A was 334 days (95% CI: 191—418) and 304 days (95% CI: 196—393) for arm B (see Fig. 2).

3.3. Toxicity

All patients (except one that was not treated) were eligible for safety analysis: 51 patients in arm A receiving 190 cycles, and 48 patients in arm B with 172 cycles. Haematologic toxicity was frequently

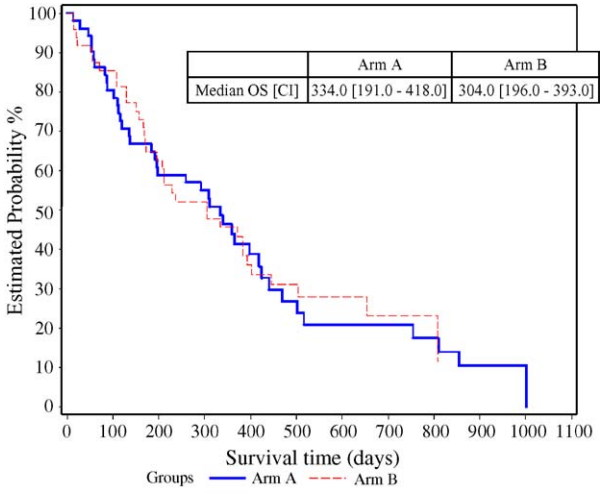

Fig. 2 Overall survival ITT population.

Table 3 Haematologic toxicity % of cycles—ITT population

% of cycle	Arm A ($N = 190$)				Arm B ($N = 172$)			
Grade	1	2	3	4	1	2	3	4
Neutrophils	16	20	22	8	4	11	31	47
Platelets	19	14	14	7	3	2	1	0
Haemoglobin	34	18	8	5	17	28	8	2
Febrile neutropenia	0	1	1	1	0	5	4	3

Table 4 Non-haematologic toxicities % of patients—ITT population

% of patients	Arm A ($N = 51$)		Arm B ($N = 48$)	
Grade	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea/vomiting	36	2	46	14
Bleeding	10	12	4	0
Asthenia	44	14	50	2
Constipation	20	2	28	4
Neuropathy	4	0	15	0
Cardiac	2	2	4	4
Alopecia	10	0	12	0
Diarrhea	12	0	8	0
Mucositis	4	2	4	6
Infection	20	8	28	14
Liver	2	2	0	2
Cough/dyspnea	16	0	6	2

observed in both arms, but as expected, the toxicity profile was different: neutropenia were mainly observed with PV, grade 4 neutropenia in 47% of cycles and 73% of patients, versus 8% of cycles and 25% of patients with GC. Febrile neutropenia occurred in 2% of patients treated by GC and 10% of patients treated by VP. However, grade 4 thrombocytopenia occurred in 7% of cycles and 18% of patients in the GC arm, while no grade 4 was observed in the reference arm. Anemia was not frequent. Grade 4 was observed in 5% of cycles in arm A, and 2% in arm B (see Table 3). Regarding the non-haematologic toxicities, some severe adverse events were observed: one patient died with a cardiac toxicity in the GC arm; three patients treated in arm B died: one severe infection, one cardiac complication and one with ''neurocentral'' toxicity. Nausea and vomiting were more frequent in the VP arm (see Table 4).

3.4. Drug delivery

A total of 190 cycles with a median number of 4 (1—5) were administered in arm A, and 172 cycles and median number of 3 (1—5) in arm B. Treatment was delayed for 13.7% of cycles in the GC arm and in 19.2% of cycles in the VP arm. However, the median number of days per cycle was 21 days in both options. The ratio between theoretical duration of chemotherapy and real duration calculated is 95.1% for GC and 93.8% for VP. The dose intensities for each delivered drug are detailed in Table 5.

4. Discussion

This randomized phase II study was designed to test the efficacy and tolerability of gemcitabine—carboplatin combination in a 3-week schedule. This schedule was established after a previous phase I study conducted by the same group of investigators [15]. This study suggested that the 3 week schedule, with gemcitabine on days 1 and 8 and carboplatin on day 1 was safe and allowed high doses for gemcitabine, despite the fact that the maximum tolerated dose was not reached with carboplatin AUC 6 mg/mL and gemcitabine 1500 mg/m^2, the recommended dose for further studies is carboplatin AUC 6 mg/mL/min on day 1 plus gemcitabine 1250 mg/m^2 on days 1 and 8 in a 3-week cycle. Thus, we decided to conduct a subsequent phase II trial in our program following these recommendations. To avoid population selection bias, a randomized phase II study was initiated, testing two regimens:

Table 5 Number of cycles (ITT population)

	Arm A ($N = 51$)	Arm B ($N = 48$)	Overall ($N = 99$)
Number of cycles	190	172	362
Mean Nb cycles per patient (S.D.)	3.7 (1.3)	3.6 (1.4)	3.7 (1.3)
Median Nb cycles per patient (S.D.)	4.0 (1—5)	3.0 (1—5)	3.0 (1—5)
Median duration of a cycle (days)	21 (21—37)	21 (21—35)	21 (21—37)
Gemcitabine (% planned dose)	83.3	—	83.3
Carboplatin (% planned dose)	100	—	100
Vinorelbine (% planned dose)	—	66.7	66.7
Cisplatin (% planned dose)	—	99.7	99.7
Cycles delayed (%)	13.7	19.2	16.3

gemcitabine—carboplatin combination as established by the GFPC's phase I study and standard treatment vinorelbine—cisplatin.

Patients' characteristics were similar in the two treatment arms, even if some prognostic factors could slightly favor the vinorelbine—cisplatin combination: weight loss and the age of the patients were lower in this arm. Furthermore, we observed a small difference in histology between the two arms: there were more adenocarcinoma types in arm A, and more squamous cell carcinomas in arm B. These observations were not statistically significant. There was the same proportion of stage IV diseases and of good performance status in both arms.

In terms of efficacy, the overall response rate of 19.6% was low in the gemcitabine—carboplatin arm and seems lower than the objective response rate obtained in other trials conducted with a similar schedule. These studies showed an objective response from 23 to 42% [21—25] whether or not they were randomized. In comparative studies, response rates have always been similar or even better with GC compared to standard treatment. According to the protocol, the response rate of 19.6% is too low to plan a randomized phase III study.

In terms of time to progression and overall survival, the results of both arms in this study are similar with a median time to progression of 140 days (72—218) in arm A and 148 days (118—210) in arm B, and median overall survival of 334 days (191—418) for GC and 304 days (196—393) for VP. These data appear equivalent to those obtained in similar phase II studies conducted with gemcitabine—carboplatin combination [23,26—29]. In these phase II studies, whether randomized or not, the median TTP and OS, varied from 3.9 to 6 months and 9 to 13 months, respectively. Despite the fact that a direct comparison is difficult between different studies, our results appear consistent with the literature.

Overall, the treatment was well tolerated and the dose administrations were rarely delayed. However, in the standard vinorelbine—cisplatin combination treatment, the most frequent toxicity observed was neutropenia, with grade 3 in 31% of cycles and grade 4 in 47% of cycles. Moreover, febrile neutropenia occurred in 12% of cycles in the VP arm versus 3% in the GC arm. Consequently, the dose intensity for vinorelbine was low with only an effective received dose at 67.7% of the planned dose. Neutropenia is a common toxicity observed with this treatment option and previous studies have suggested a reduction in the dose of vinorelbine from 30 mg/m^2/week to 25 mg/m^2/week. With the current study, we confirm that optimal dosage for vinorelbine in a VP combination should be 25 mg/m^2 on days 1 and 8 on a 3-week schedule.

Thrombocytopenia was the main problem in the GC arm. This toxicity (grade 3/4 in 21% of cycles) was sometimes complicated (bleeding grade 2/3 in 5% of cycles) and did not seem to have an impact on the treatment schedule with a received gemcitabine dose of 84.9% of the planned dose. The non-haematologic toxicity profile was mild. The GC arm did not show any severe toxicity, mainly represented by asthenia, anorexia, bleeding and dyspnea; a transient rise in liver enzymes was rare. This toxicity profile is similar to the toxicity observed in previous studies with the same design and despite lower dosages used for this combination in the other trials, the tolerance remains acceptable [26,29]. These finding confirm the feasibility of this treatment given at these proposed dosages for both drugs.

Toxicities observed in the VP arm were mainly nausea-vomiting, constipation, neuropathy, fever and infection. Six toxic deaths were deplored in the VP arm: two fatal cardiac events, two severe infections, and two neurocentral failures. Two patients died after one course in the GC arm, one after a cardiac accident and one for an unknown reason.

The GC regimen was also studied in several randomized trials versus different standard chemotherapies. In a recent study [25], this combination was shown to be better tolerated than MIP (mitomycin, ifosfamide and cisplatin), with a significant survival advantage (median survival time of 10 months compared to 7.6 months). No advantage of the GC combination was ever described when compared to mitomycin, vinblastine and cisplatin (MVP) [21]. However, the combination showed a higher therapeutic response, an improved 1-year survival rate and a similar toxicity profile to the classic vinblastine—cisplatin combination [24]. A recently published meta-analysis (including our own study) showed a small but statistically significant gain in survival with a translation in clinical improvement for patients treated by gemcitabine—platinum regimens when compared to other standard platinum-based regimens [30]. This activity, at least similar to standard treatments, and with its favorable toxicity profile make this combination an interesting option for the treatment of patients with advanced NSCLC, especially when an hospitalization is not warranted. This combination may also be used for elderly patients with NSCLC, but with a low dose of carboplatin. A recent study [31] demonstrated that combining gemcitabine 1250 mg/m^2 on days 1 and 8 (always in a 3-week schedule) to carboplatin AUC 4 on day 1, is safe with a manageable toxicity and an interesting efficacy (time to progression of 8 months).

4.1. Conclusion

With regards to this randomized phase II study, the gemcitabine—carboplatin combination has shown efficacy, in terms of median survival time and median time to progression, in the same range as other combinations with a good tolerance profile. Gemcitabine—carboplatin in a 3-week schedule represents an interesting alternative treatment for patients with advanced non-small cell lung cancer. The preference for this treatment could be influenced by its easy administration on an outpatient basis and with a better overall toxicity profile. However, efficacy of this combination in terms of objective response rate, according to the statistical hypothesis, is not sufficient to warrant a further randomized phase III study.

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