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Gemcitabine, cisplatin and vinorelbine as induction chemotherapy followed by radical therapy in stage III non-small-cell lung cancer: a multicentre study of galician-lung-cancer-group

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Abstract

Purpose: To determine the effectiveness of a gemcitabine–cisplatin–vinorelbine combination in patients with stage III non-small-cell lung cancer (NSCLC). *Patients and methods:* Patients ($n = 46$) with stage III NSCLC and naive of therapy were recruited into the trial to receive gemcitabine (G, 1000 mg/m^2) on days 1 and 8, cisplatin (C, 100 mg/m^2) on day 1 and vinorelbine (V, 25 mg/m^2) on days 1 and 8 every 21 days for three cycles. *Results:* Two patients achieved complete response (CR) and 23 partial response (PR), overall response 52%. Subsequent radical surgery included nine patients of whom four were non-resectable and five were resected and with 1 CR. Radiotherapy was administered to 31 patients, and two achieved CR. The median time to progression and overall survival were 37 and 50 weeks, respectively. Grade 3–4 neutropenia and thrombocytopenia occurred in 35% of cycles, with two toxic deaths. Severe non-haematological toxicity was uncommon. *Conclusions:* This GCV combination is effective in patients with stage III NSCLC, and with an acceptable toxicity.

Keywords: Gemcitabine; Vinorelbine; Cisplatin; Non-small-cell lung cancer

1. Introduction

Lung cancer is the leading cause of cancer death in males and ranked third in females in developed countries. Approximately 80% of new cases of lung cancer are non-small-cell lung cancer (NSCLC) and over 70% of patients are diagnosed when the disease is advanced (stages IIIB and IV). Over 80% of patients die within the 1 year after diagnosis and the survival rate at 5 years is around 13% [1]. In patients with stage III disease, two randomised trials of neoadjuvant chemotherapy and subsequent surgery [2,3] have demonstrated an increase in survival as well as in the disease-free interval. Hence, neoadjuvant chemotherapy (with or without radiotherapy) is generally used in these patients prior to surgery [4]. Patients with tumours considered non-resectable are treated only with chemotherapy and/or radiation ther-

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apy. The recommendations of the American Society of Clinical Oncology (ASCO, 1997) indicate that, with improved survival as the objective, chemotherapy in combination with radiotherapy provides the treatment-of-choice for selected patients with NSCLC which is locally advanced and non-resectable [5].

Among all the treatment schedules evaluated, platinum-based chemotherapy appears to increase the survival rate and to improve the quality-of-life in patients with advanced-stage disease (stages IIIB and IV) [6–8]. However, the optimum dose has not been determined yet as well as whether a 3-drug cisplatin based combination is superior to a 2-drug combination. Among the new pharmaceutical preparations available, the combinations of cisplatin with gemcitabine or vinorelbine have been shown to be particularly active. The gemcitabine–cisplatin combination has been tested in several trials and has achieved response rates of 21–40% with a median survival ranging from 8 to 9 months [9–12]. The cisplatin–vinorelbine combination has achieved acceptable results in phase III trials with response rates around 26–30% and median survival time of 8–9.3 months [13–16]. The combination of gemcitabine–vinorelbine–cisplatin triplet is attractive because of the different, possibly synergistic, modes of action involved as well as the manageable toxicity. However, the combination has been poorly studied, to date. In a phase I study testing this regimen, the Southern Italy Cooperative Oncology Group [17] obtained a 52% of overall response rate and a 51% 1 year survival rate. Based on these results, we began a multi-centre study to better define the activity and toxicity of this regimen in patients with stage III NSCLC who are scheduled for subsequent radical treatment (surgery or radiotherapy).

2. Patients and methods

2.1. Eligibility criteria

Chemotherapy-naive patients with histology or cytology-confirmed stage IIIA or IIIB NSCLC (without malignant pleural or pericardial effusion) were eligible for this trial. All patients with stage IIIA disease had clinically visible N2 disease. Mediastinoscopy was optional. No prior thoracic radiotherapy was allowed. Patients were required to have: adequate bone marrow function (neutrophil count $\geq 1.5 \times 10^9$ per l, platelet count $\geq 100 \times 10^9$ per l and haemoglobin level ≥ 100 g/l); adequate liver function (bilirubin level 1.25 times the upper limit of normal (ULN); AST, ALT and GGT $< 3 \times$ ULN); adequate renal function (serum creatinine within the reference range and/or creatinine clearance ≥ 60 ml/min); performance status ≤ 2 of the Eastern Cooperative Oncology Group (ECOG) scale; a life expectancy of at least 12 weeks; bi-dimensionally measurable lesions ≥ 2 cms according to the World Health Organisation (WHO) criteria; and to be between 18 and 75 years of age. The clinical characteristics of the patients are summarised in Table 1. All patients gave fully informed written consent. Patients who were pregnant or were breast-feeding or who had a serious concomitant systemic disorder or a second malignancy were excluded from the study.

2.2. Diagnostic procedures

Pre-treatment evaluation included a complete history and physical examination, electrocardiogram, chest X-ray, fiberoptic bronchoscopy and computed tomography scans of the chest and upper abdomen. Mediastinoscopy was permitted but not routinely performed. Other studies (brain CT or bone scanning) were optional, according to the clinical manifestations of each patient.

Laboratory investigation included a complete blood cell count, full chemistry profile, prothrombin time and urinalysis. Physical examination, ECOG performance status and chest X-ray were performed on the first day of each chemotherapy course. Haematology and biochemistry were repeated weekly. All the other procedures necessary to evaluate response-to-treatment were performed after three courses.

2.3. Treatment regimen

The treatment schedule of the gemcitabine–cisplatin–vinorelbine (GCV) combination was: gemcitabine (1000 mg/m^2 in 500 ml physiologic saline) as a 30 min infusion on days 1 and 8, cisplatin (100 mg/m^2 in 1l physiologic saline) as a 60 min infusion on day 1, and vinorelbine

Table 1
Patient characteristics on entry into the study

Characteristic	Number	%
Gender		
Male	43	93.5
Female	3	6.5
Age (years)		
Median	63.5	–
Range	42–75	–
ECOG PS		
0	10	21
1	35	76
2	1	2
Stage		
IIIA	11	23
IIIB	35	76
Histology		
Squamous cell carcinoma	32	69
Adenocarcinoma	9	19
Large cell carcinoma	5	11

(25 mg/m^2 in 100 ml physiologic saline) as a 10 min infusion on days 1 and 8 of the cycle. Each cycle was of 3 weeks duration. On day 1, before starting drug administration, the patients received intravenous hydration with 1 l normal saline and anti-emetic prophylaxis with a 5-hydroxitryptamine receptor antagonist together with 20 mg of dexamethasone. During cisplatin administration manitol was indicated and, following drug administration, 1 l normal saline was infused over a period of 60-min. Oral hydration was indicated at home. On day 8, no pre/post-hydration was performed and anti-emetic prophylaxis was with metoclopramide together with 12 mg of dexamethasone. All treatment was performed on an outpatient basis. Prophylaxis with growth factors for neutropenia was not allowed within the study protocol.

Each cycle started every 21 days if the neutrophil count was $\geq 1.5 \times 10^9$ and the platelet count was $> 100 \times 10^9$ per l. If neutrophil and platelet counts on day 1 of treatment were less than these values, the scheduled treatment was defered for 1 week. The patient was taken off the protocol if no improvement in these values occurred after a further week of delay. Vinorelbine and gemcitabine were administered at 80% of the planned doses if grade 2 neutropenia or grade 1 thrombocytopenia occurred on day 8. In case of grade 3–4 neutropenia or thrombocytopenia grade ≥ 2, the scheduled session was omitted. The doses of both drugs were also reduced by 20% if grade 4 neutropenia or thrombocytopenia or grades 3–4 non-haematologic toxicity had occurred in the previous cycle. The doses of vinorelbine and cisplatin were reduced by 20 and 50%, respectively, if grade 2 neuropathy occurred. The patient was transferred out of the study if grade 3 or 4 neuropathy occurred. Cisplatin was delayed for 1 week if serum creatinine levels exceeded 200 mmol/l or the creatinine clearance was < 40 ml/min. If these levels persisted, the treatment was concluded and the patient was taken off the study.

2.4. Response and toxicity evaluation

Patients underwent tumour response assessment after three courses. The evaluations included clinical examination, chest X-ray and computed tomography scans of the chest and upper abdomen. The standard WHO criteria were followed for defining response. Following the response assessment and in a multidisciplinary session including a radiologist, a thoracic surgeon, a clinical oncologist and an radiation oncologist, an evaluation of the patient was made in relation to the subsequent treatment options (surgical intervention, radiotherapy, continuation of chemotherapy or support care). At this moment the local treatment was determined. Early progression was considered as treatment failure, and it was permitted radiotherapy or other chemotherapy regimen at investigator criteria. Time-to-progression was measured from the start of treatment until disease progression, and survival from initiation of chemotherapy until death or the date of last follow-up. Survival and time-to-progression curves were estimated by the Kaplan–Meier product-limit method. Toxicity was evaluated according to the Common Criteria Toxicity of the National Cancer Institute (CTC-NCI) grading system. Data were collected weekly (days 1, 8 and 15). Fatigue was evaluated on the following scale: grade 0, none; grade 1, capacity to continue with normal daily activities; grade 2, incapacity to perform normal daily activities or requiring looking-after for $< 50\%$ of the time; grade 3, in bed or chair and requiring looking-after for $> 50\%$ of the time; grade 4, completely confined to bed or incapable of any personal self-help.

3. Results

Between January 1998 and 1999, a total of 46 consecutive NSCLC patients (11 at stage IIIA and 35 at stage IIIB) were enrolled at seven participating oncology departments. The majority of patients were male (93%) and the median age was 63.5 years (range 42–75 years). The most frequent histology was squamous cell carcinoma (70% of cases). In total, 135 cycles were administered (median of three cycles per patient) and the median and mean dose intensity was 100 and 90% of projected, respectively. In seven patients, dose intensity was under 80%. All patients were evaluable for toxicity and five patients were not evaluable for response: two toxic deaths, two patients decided not to continue with treatment after having recovered from toxicity, and one patient discontinued early because of severe toxicity. On an intention-to-treat analysis there were two clinical complete responses (CR) and 22 partial responses (PR) with an overall response rate of 52% (95% CI: 37.7–66.5). After chemotherapy seven patients were downstaged at CT scan. There was stable disease (SD) in 14 patients (30%) and three patients (7%) had progressive disease (PD). These results are summarised in Table 2. The overall response rate was 58.5% in those patients who were evaluable for response.

Nine patients, six at stage IIIA (two SD; four PR) and three at stage IIIB (all PR) were operated-upon with radical intent, after the committee evaluation. In five of these patients the tumour was resectable resulting, in one pathological CR, while four patients were non-resectable (resectability rate of 55.5% in these nine patients). A staged IIIA patient, potentially resectable, did not go to surgery by worsening of the respiratory function. In addition, this patient and another 30 received radiotherapy with two new CR in patients who were PR after chemotherapy. At progression, five patients received a taxane in second line chemotherapy.

Table 2
Response to treatment on intention-to-treat analysis ($n = 46$)

Results		Number	%
Non-evaluable		5	10
	Voluntary withdrawal	2	4
	Discontinued early	1	2
	Toxic death	2	4
Overall response		24	52
95% CI		38–67	
	CR	2	4
	PR	22	48
	SD	14	30
	PD	3	7

Table 3
CTC-NCI grading toxicity per cycle observed during the study

Side-effect	Grade (%)			
	I	II	III	IV
Haemoglobin	44	26	2	0
Neutrophils	13	12	14	13
Platelets	16	8	6	1.5
Nausea	18	37	3	0
Vomiting	13	2	7.5	1.4
Creatinine	0	0.7	1.5	0
Stomatitis	1.5	2	0.7	0
Diarrhoea	0	0.7	0	0
Cardiac function	0	0.7	0.7	0
Dyspnea	0	0	0	0.7
Transaminases	0	0.7	0.7	0

With a median follow-up of 84 weeks (range 58–113 weeks) 11 patients are still alive and five are progression-free disease. The median time-to-progression was 37 weeks (95% CI: 26–48+) and the overall survival time was 50 weeks (95% CI: 37–63+) (Fig. 1). Survival at 1 year was 51% of patients.

3.1. Toxicity

The most notable toxicity was haematological. Grade 3–4 neutropenia, thrombocytopenia and anaemia occurred in 27, 7.5 and 2% of cycles, respectively (Table 3). There were 16 hospitalisations, seven due to neutropenic fever and nine because of other causes (one of non-febrile neutropenia, three for vomiting, one for dyspnea, two for renal toxicity, one for cardiac insufficiency and one for acute cerebrovascular accident but who subsequent recovered). Two patients received red blood cell transfusions (2 U per patient). Two toxic deaths occurred, one due to neutropenic fever and pneumonia after the first cycle of treatment and the other one at home from unknown causes following the second chemotherapy cycle. Two patients refused further treatment after having recovered from serious toxicity (one after febrile neutropenia and liver toxicity and the other one after heart failure and shock). One patient was excluded from the study because of grade 3 renal toxicity which was not resolved. Overall toxicity was greater and more frequently observed in patients above 65 years. Severe non-haematological toxicity was uncommon, with grade 3–4 vomiting in 9% of cycles, grade 2 alopecia in 4.5% of patients and sensorial neuropathy in 6.5% of patients. Fatigue grade 1, 2 and 3 was reported in 15, 15 and 13% of patients, respectively.

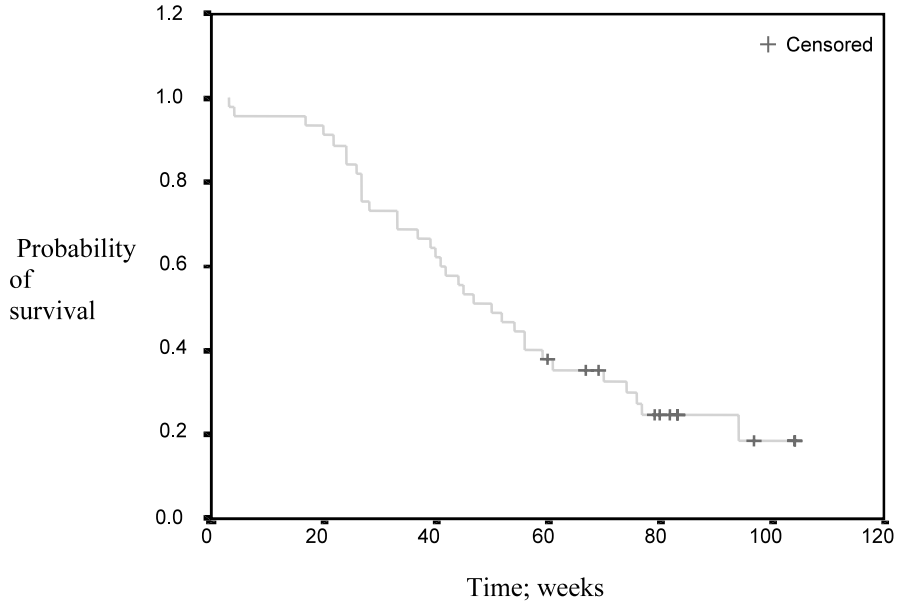

Fig. 1. Overall survival.

4. Discussion

This multicentre study was designed to evaluate activity and toxicity of a cisplatin, gemcitabine and vinorelbine combination, followed by radical treatment, based on the results of a phase I trial conducted by the Southern Italy Cooperative Oncology Group [17]. In that study 31 stage III–IV NSCLC patients were treated with cisplatin 50 mg/m^2, gemcitabine 1000 mg/m^2 and vinorelbine 25 mg/m^2 on days 1 and 8 every 3 weeks (CGV). It is not known the best secuence between gemcitabine and cisplatin. We decided to modify the sequence of the Italian study and to administrate gemcitabine before cisplatin on day 1 because theoretical models and pharmaco-dynamic studies indicated that this schedule had greater synergistic action [18–20]. Also, the sequence (GCV) of gemcitabine before cisplatin appears to be more favoured by investigators [10,12].

With their triplet, the Italian group obtained a 52% overall response rate with 51% 1 year survival and a manageable toxicity, principally neutropenia in 24% of the cycles, which was manageable. In a subsequent randomised phase II trial [21] the same group of investigators compared the activity of their CGV triplet versus cisplatin, epirubicin and vindesine in advanced NSCLC. In 87 patients included, the response rate was 57% in the group with CGV versus 37% in the other treatment arm with a median survival of 50 and 33 weeks, respectively. The toxicity was, essentially, haematological with neutropenia and thrombocytopenia in 46 and 14% of the patients, respectively. Based on these results, the next step taken by the Southern Italy Cooperative Oncology Group was to design a phase III study in patients with the same characteristics [22,23]. There were 343 patients included in four treatment arms: cisplatin–gemcitabine (CG), cisplatin–vinorelbine (CV), cisplatin–gemcitabine–paclitaxel (CGT) and CGV. The CGT and CGV arms achieved response rates of 48 and 44% with a median survival of 51 and 38 weeks, respectively. There were statistically significant differences in favour of the 3-drug combination (CGT and CGV) compared with the 2-drug schemes (CG and CV). The authors proposed these 3-drug combinations as the standard for the treatment in patients <70 years and with a PS of 0–1. Ginopopulos et al. [24] in a phase II trial using gemcitabine 1000 mg/m^2, vinorelbine 25 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 on day 8 obtained a 65% response rate (19% CR) in 31 patients with stage IIIB–IV. The median survival was 56 weeks and 65% of the patients survived at 1 year. In 77% of the patients, there was leuconeutropenia grade 3–4. The use of colony stimulating factors and erythropoietin was allowed within the protocol to maintain dose intensity.

The Spanish Lung Cancer Group [25] designed a multi-centre phase III trial for stage IIIB (malignant pleural effusion) or stage IV NSCLC patients. The chemotherapy arms were: cisplatin 100 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 (arm A); cisplatin 100 mg/m^2 and gemcitabine 1000 mg/m^2 and vinorelbine 25 mg/m^2 on days 1 and 8 (arm B); gemcitabine 1000 mg/m^2 and vinorelbine 30 mg/m^2 on days 1 and 8 for three cycles followed by ifosfamide 3 g/m^2 and vinorelbine 30 mg/m^2 on days 1 and 8 (arm C). In the 562 patients, recruited response rate and median survival were 41% and 40.8 weeks, 40% and 34.4 weeks, and 24.1% and 44.8 weeks for the A, B and C treatment arms, respectively. Again, the principal toxicity was haematological.

Our study, initiated before the publication of the majority of these above-mentioned trials, shows similar results, but in a different group of patients. So that, direct comparisons between results need to be conduced cautiously since the study populations were different and did not include any patients with stage IIIA disease. To our knowledge there are not published studies with this schedule and in this patient population. The classical studies and those with new drugs conducted in patients with stage IIIA NSCLC indicated objective response above 50% (range 50–85%) with a very variable percentage of CR (0–20%). The rate of resectability was from 35 to 75% and median survival around 18 months (27 months in complete resections), with 25–30% 3 year survival [26]. In a phase II trial, the EORTC studied the gemcitabine–cisplatin combination in stage IIIA N2 NSCLC patients. In this study, 47 patients were included, and the response rate was 70% (in 38 patients that completed treatment), with 71% complete resections in 17 patients randomised to surgery. Median survival was 18.9 months with 69% 1 year survival. [27]. The overall data of our study are similar to those usually observed in stage IIIB but are lower than those presented for stage IIIA disease. Nevertheless, it is well known that patients with clinical N2 disease have poorer prognosis than those identified during surgery. In our study, only 11 of the 46 patients were stage IIIA and these patients had clinically visible N2 disease which could explain our slightly poorer results. Since radical management of these patients is logical, most of them received radiotherapy or subsequent surgery. Therefore, the precise effect of the chemotherapy on survival time is difficult to assess. We must consider that overall survival will be influenced by induction chemotherapy, local treatment and possible second line chemotherapy.

The scheme was moderately toxic and was mainly confined to neutropenia and thrombocytopenia. Of note is that seven patients needed hospitalisation for febrile neutropenia and there were two toxic deaths. Fatigue was no directly related to anemia. Only four of 13 patients with grade 2–3 fatigue had grade 2 haemoglobin, and none of them had greater haemoglobin toxicity. Fatigue had negative consequences in patients' reported

quality of life, although the effect was temporal. The most severe toxicities occurred in patients older than 65 years and the levels are somewhat lower than those in other publications. Extra-haematological toxicity consisted, essentially, of nausea, vomiting and fatigue but there was a very slight incidence of neuropathy. We consider that these toxicity levels are acceptable in these patients with radical treatment intention but not in the palliative setting.

In conclusion, we believe that in the patient population studied, the combination and sequence of gemcitabine, cisplatin and vinorelbine is effective and active. The toxicity levels are moderate and well tolerated in patients younger than 65 years. On the basis of the recent data presented, we think that we are near to the maximal response rates with chemotherapy alone. This is why our group is developing studies with new induction chemotherapy regimens and other combination strategies for NSCLC.

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