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ORIGINAL ARTICLE

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Gemcitabine, ifosfamide and Navelbine (GIN): a platinum-free combination in advanced non-small-cell lung cancer (NSCLC)

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Abstract *Purpose*: To evaluate the activity and toxicity of gemcitabine, ifosfamide and Navelbine (GIN) in advanced NSCLC. *Patients and methods*: Stage IIIB/IV NSCLC, WHO performance status <2 and bidimensionally measurable disease were required to enter the study. Gemcitabine 1000 mg/m^2 day 1 and 1000 or 800 mg/m^2 day 4, ifosfamide 3 g/m^2 day 1 (with mesna), Navelbine 25 mg/m^2 day 1 and 25–20 mg/m^2 day 4 were administered on an outpatient basis every 3 weeks for a maximum of six courses. Objective remissions (ORs) were evaluated every two courses. According to Simon's optimal two-stage design, more than 18 ORs out of 54 patients were required to establish the activity of this regimen. *Results*: The study group comprised 50 patients. Most patients had metastatic disease (79%) and nonsquamous histology (71%). The total number of courses administered was 200, with a median per patient of 4 (range 1–6). Myelosuppression, in particular leukopenia, was the most frequent toxicity: grade 3–4 neutropenia (WHO) occurred in 47% of the courses, while grade 3–4 thrombocytopenia and anemia affected, respectively, 6.6% and 3.5% of the courses only. Twelve episodes of febrile neutropenia were recorded, and three patients required hospital admission. No toxic deaths were reported. Nonhematological toxicity was generally mild and not clinically relevant. A total of 25 ORs (1 complete response and 24 partial responses) were obtained for a response rate of 52% (95% CI 37.4–66.5%). One-year survival was 46.5%. *Conclusions*: The GIN combination showed promising activity against NSCLC with myelosuppression, in particular neutropenia, being dose limiting. This non-platinum-based triplet may be a valuable alternative to standard platinum-containing regimens and it is under evaluation in an ongoing randomized trial.

Keywords Metastatic non-small-cell lung cancer · Non-platinum-based triplet · Ifosfamide

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Introduction

The 1990s was the most productive decade for the development of chemotherapy in advanced non-small-cell lung cancer (NSCLC). In 1995 the Non-Small-Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer which established that, in first-line treatment, the cisplatin-based regimens of the 1980s were superior to best supportive care and the improvement in survival was primarily attributed to cisplatin (CDDP) in all patient categories. No recommendations could be made on specific cisplatin-containing chemotherapies [1]. The clear role of platinum-based combinations was further supported by the results of prospective randomized trials [2, 3]. Furthermore, unlike the prior, in the 1990s an abundance of novel active agents for the treatment of lung cancer were identified: vinorelbine (Navelbine), gemcitabine, docetaxel, paclitaxel and irinotecan have all shown promising activity as single agents, and their combinations with cisplatin have become the recommended standard of care in this disease [4]. However, the palliative nature of

treatment, the severity of cancer-related symptoms, the comorbidities and the unfavorable side-effect profile of cisplatin make its administration unacceptable, difficult or sometimes impossible in many patients. Nevertheless, the availability of new active agents, along with the need for better-tolerated combinations, have fostered further investigation in the area of platinum-free regimens.

In designing combinations for the treatment of NSCLC the reproducible activity of each component is a minimal prerequisite. On these grounds we carried out a phase II study aimed at defining the antitumor activity and toxicity profile of a non-platinum-based triplet consisting of gemcitabine, ifosfamide and Navelbine (GIN) in patients with advanced NSCLC. All the three drugs show high antitumor activity as single agents with a favorable toxicity profile. Gemcitabine shows a reproducible response rate of approximately 20% in patients with untreated NSCLC. At standard doses, gemcitabine administered weekly is associated with a low incidence of side effects, which include myelosuppression, nausea, vomiting and alopecia [5]. Ifosfamide, one of the most active among the old drugs, shows a response rate of 20% to 32% when administered as a single agent in previously untreated patients [6]. Finally, the activity and efficacy of Navelbine have been very well demonstrated in phase II and III clinical trials as a single agent or in combination with platinum compounds [7, 8]. The significant antitumor activity along with the favorable toxicity profile of these agents prompted their use in combination.

Patients and methods

Chemotherapy-naive patients with stages IIIB (pleural effusion and/or supraclavicular nodes)/IV NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status <2 were included. Patients were required to have bidimensionally measurable disease, adequate pretreatment hematological function (WBC count $\leq 4000/\mu l$, hemoglobin >10 g/dl), hepatic function (bilirubin not more than twice the normal level) and renal function (creatinine not more than twice the normal limit). Symptomatic brain metastases was an exclusion criterion. Staging procedures consisted of: bronchoscopy, chest radiograph, CT scan, abdominal ultrasound performed within 4 weeks before the beginning of the treatment (other types of organ-specific scanning were optional but recommended in cases of symptoms). Restaging was planned every two courses of chemotherapy by repeating the same tests used at study entry. Objective remissions (evaluated according to WHO criteria [9]) were reviewed extramurally and confirmed 4 weeks apart. During the whole therapeutic program patients were evaluated weekly for toxicity according to WHO recommendations.

Written informed consent was obtained from all patients according to local institutional policies. The study was approved by the local IRB/ethical committee of participating institutions and was conducted according to GCP.

The original chemotherapy protocol consisted of: Navelbine 25 mg/m^2 day 1 and day 4, gemcitabine 1000 mg/m^2 days 1 and 4 and ifosfamide 3 g/m^2 (infused over 2 h) day 1. Mesna (sodium 2-mercaptoethane sulfonate) was administered as uroprotection. Since three cases of neutropenic fever were recorded among the first eight patients enrolled, the protocol was amended by reducing the dose of Navelbine and gemcitabine on day 4 to 20 mg/m^2 and 800 mg/m^2, respectively. Courses were repeated every 3 weeks on an outpatient basis. White blood cell counts (WBC) were performed weekly and biochemistry was determined on day 1 of each cycle. Chemotherapy on day 4 was administered with no WBC determination. In cases of grade 4 neutropenia, ciprofloxacin 500 mg orally twice a day and fluconazole 100 mg daily were administered until ANC $>1000/\mu l$. The prophylactic use of colony-stimulating factors (CSFs) was not allowed while their therapeutic use was suggested for febrile neutropenia. In cases of grade 3/4 thrombocytopenia or febrile neutropenia a 25% reduction in the doses of the three drugs administered on day 1 was performed in subsequent courses of chemotherapy.

Simon's optimal two-stage design for phase II clinical trials was used to calculate the sample size [10]: P0 (clinically uninteresting true response rate) and P1 (sufficiently promising true response rate) were set at 20% and 40%, respectively. In the first stage, 19 patients had to be included: if four or fewer responses were observed, accrual was stopped, otherwise 35 additional patients had to be registered. The drug combination was considered of interest if more than 18 responses were observed out of 54 evaluable patients. Time to progression was calculated from the date of registration to the evidence of progression. Survival was measured from the date of registration to death. Survival and time to progression were estimated using the Kaplan-Meier method [11].

Results

The study group comprised 50 chemotherapy-naive patients. Accrual into this study was stopped as soon as the number of responses required by the statistical design was achieved. Two patients were excluded from the analysis: one was ineligible (age >70 years) and the other was never treated. The characteristics of the remaining 48 evaluated patients are listed in Table 1.

Toxicity data are shown in Table 2 as the worst toxicity grade per course. A total of 200 courses of chemotherapy were administered (median per patient 4, range 1–6). Myelosuppression was the toxicity most frequently reported: grade 4 neutropenia was observed in 21.6% of the courses, while grade 4 thrombocytopenia was observed in only 2.5% of the courses. Twelve episodes of febrile neutropenia were recorded, and three patients were admitted for parenteral antibiotics. Three patients required early discontinuation of chemotherapy, two because of worsening performance status (after the fourth and fifth course, respectively) and one because of severe skin rash. Nevertheless, compliance with the treatment

Table 1. Patient characteristics

No. of patients evaluated	48
Age (years)	
Median	63
Range	44–69
ECOG performance status	
0	31 (64.6%)
1	17 (35.4%)
Stage	
IIIB	10 (20.8%)
IV	38 (79.2%)
Histology	
Squamous	14 (29.2%)
Non-squamous	34 (70.8%)

Table 2. Worst toxicity per course (WHO)

	Grade 3 (%)	Grade 4 (%)
Leucopenia	20.5	6.6
Neutropenia	25.2	21.6
Thrombocytopenia	4.1	2.5
Anemia	3.5	–
Vomiting	2.5	–
Skin rash	1.3	–
Alopecia	4.6	–

was good and the average over the planned chemotherapy dose delivered was 98%. No toxic deaths were observed.

In the first step, 10 out of 19 patients achieved a clinical remission. The second step was initiated, and 25 objective responses (24 partial responses and 1 complete response) were obtained among the first 48 patients, with a response rate of 52% (95% CI 37.4–66.5%). Accrual was stopped at this point as we had already exceeded the statistical requirements. Disease stabilization was observed in 14 patients (29%) and 6 patients showed progression of disease while on treatment. Three patients were not evaluable for response as they had received fewer than two courses of chemotherapy; however, according to the "intention to treat" policy, they were included in the response analysis as failures. All objective remissions were reviewed extramurally and confirmed at least 4 weeks apart. Median time to progression and median overall survival were 7.1 (95% CI 5.5–9.9) and 11 months (95% CI 9.6-NA), respectively. One-year survival was 46.5%.

Discussion

In the early 1990s, a revolution took place in the options for NSCLC treatment: the role of cisplatin-based chemotherapy was firmly established and several newer drugs were introduced into clinical practice. The new agents showed interesting antitumor activity often coupled with a favorable toxicity profile. With the turn of the century, the need for better-tolerated regimens along with an interest in establishing a clear therapeutic role for these new agents, have opened the era of non-platinum-containing combinations.

On these grounds we performed the present phase II study in which the three drugs, gemcitabine, ifosfamide and Navelbine, with single-agent activity in NSCLC, were tested in combination in advanced disease. The choice of the "triplet" was based on the encouraging results obtained in our previous experience with the regimen vinorelbine, ifosfamide, cisplatin (VIP) in the same subset of patients [12, 13]. Cisplatin was replaced with gemcitabine in order to avoid cisplatin-related acute and late toxicities and to abolish hyperhydration and forced diuresis, while maintaining high antitumor activity. The schedule days 1–4 allowed the delivery of full doses of the two drugs, with no further reduction due to hematologic toxicity. Chemotherapy actually administered was 98% of that planned, with good treatment compliance in the majority of patients. Myelosuppression, in particular neutropenia, was the dose-limiting toxicity; however, grade 3–4 neutropenia was generally of short duration and successfully manageable on an outpatient basis. None of the patients experienced peripheral neuropathy or renal failure, while 9 out of 48 patients (18%) experienced cumulative grade 3 fatigue.

The excellent antitumor activity of the GIN regimen (52% response rate) is particularly interesting considering that, in our series, the majority of patients had metastatic non-squamous lung tumors, suggesting that cisplatin may not be an essential component in the chemotherapy of these histological subtypes. In vitro experience has demonstrated that drugs such as topotecan and cisplatin are particularly active in squamous carcinoma cell lines while other drugs, including taxanes and gemcitabine, appear to have a higher antitumor activity in non-squamous tumors [14]. These in vitro data are in keeping with some clinical observations suggesting a relationship between histological subtype and probability of response to platinum-free or platinum-based regimens [15, 16]. The possibility of considering different chemotherapy regimens (platinum- or non-platinum-based) for the different histological subtypes in NSCLC should be further explored.

In terms of activity and tolerability, our results compare favorably with those of novel cisplatin-based doublets [17, 18] and triplets [19, 12]. In addition, our figures appear superior to those of doublets including the same agents as our regimen [20, 21]. The activity of the GIN regimen also compares favorably with that of other non-platinum-based triplets [22]. The encouraging activity data we obtained with this combination have also been found by other authors testing the same triplet although using a different schedule [23, 24, 25].

Rationally designed drug combinations, which do not include cisplatin, could be reasonable alternatives for patients who cannot tolerate cisplatin. However, although the efficacy of non-platinum combinations is encouraging and compares favorably with historical controls, the results of randomized trials are awaited before we will be able to change clinical practice.

The GIN regimen is now under evaluation within an ongoing prospective randomized trial assessing the role of triplets vs doublets (with or without platinum) in advanced non-small-cell lung cancer.

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