Triplets versus doublets, with or without cisplatin, in the first-line treatment of stage IIIIB–IV non-small cell lung cancer (NSCLC) patients: a multicenter randomised factorial trial (FAST)

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BACKGROUND: The FAST is a 2 × 2 factorial trial addressing two questions: (1) the role of replacing cisplatin (P) with a non-platinum agent, vinorelbine (N), and (2) the role of adding a third agent, ifosfamide (I), in a doublet based on gemcitabine (G).

METHODS: A total of 433 stage IIIB–IV non-small cell lung cancer (NSCLC) patients were randomised to one of four arms: gemcitabine–cisplatin (GP), gemcitabine–vinorelbine, gemcitabine–ifosfamide-cisplatin or gemcitabine–ifosfamide –vinorelbine. Two comparisons were performed: N- vs P-containing regimens and I-triplets vs non-I doublets.

RESULTS: For N- vs P-containing regimens, adjusted overall survival was 9.7 vs 11.3 months (P = 0.044), progression-free survival was 4.9 vs 6.4 months (P = 0.020) and response rate was 24% vs 31% (P = 0.124), respectively. No statistically significant difference was observed between doublets and triplets. Grade 3–4 haematological toxicity was significantly more frequent in P-containing therapy; grade 3–4 leucopenia was significantly more common in triplets. Concerning non-haematological toxicity, grade 3–4 nausea-vomiting was significantly increased in P-containing regimens.

CONCLUSIONS: This trial provides evidence of a slight survival superiority of GP-containing regimens over platinum-free N-containing chemotherapy. This trial also confirms that the addition of a third chemotherapy agent (I) to a standard G-based doublet does not improve treatment outcome.

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Until recently, the standard treatment of advanced non-small cell lung cancer (NSCLC) has been based on a combination of cisplatin with a third-generation chemotherapeutic agent, such as paclitaxel, docetaxel, vinorelbine or gemcitabine (Azzoli et al, 2009; D’Addario et al, 2010). These regimens obtained comparable outcome results (Kelly et al, 2001; Scagliotti et al, 2002; Schiller et al, 2002) but, among these, at least in Europe, cisplatin–gemcitabine has been the most used combination (Le Chevalier et al, 2005).

At the time this trial was designed the discussion concerning optimal chemotherapy treatment of advanced NSCLC was mainly focused on the uncertain superiority of platinum- vs non-platinum-based regimens and of triplets vs doublets. Despite its pivotal role in NSCLC management, cisplatin is associated with a number of serious side effects including nausea-vomiting, neurotoxicity and renal function impairment and it is burdened by delivery problems such as the need for prolonged hydration (Tiseo et al, 2007). To overcome these limitations, most clinicians were considering the use of carboplatin and of platinum-free combinations as a possible alternative.

Although carboplatin and cisplatin have similar mechanism of action and spectrum of activity, some trials and an individual patient data meta-analysis evidenced that cisplatin-based is slightly superior to carboplatin-based chemotherapy in terms of response...
rate (RR) and also, in certain subgroups (third-generation regimens and non-squamous histology), in terms of survival, without a significant increase in severe toxicity (Ardizzone et al, 2007).

The activity and tolerability of third-generation agents led many investigators to evaluate platinum-free doublets in the hope that platinum analogues could be spared for the treatment of advanced NSCLC (Georgoulias et al, 2001; Kosmidis et al, 2002; Gridelli et al, 2003).

Addition of a third agent to platinum-based doublet may be an option to improve outcomes in NSCLC. This strategy has been shown to be associated with superior outcomes in other malignancies (Vermorken et al, 2007). This led to the conduct of multiple trials comparing a two-drug regimen with a three-drug regimen in advanced NSCLC patients (Comella et al, 2000; Alberola et al, 2003; Laack et al, 2004; Paccagnella et al, 2006). Our group, in particular, developed two different triplets including ifosfamide, an alkylating agent with activity against NSCLC commonly used in old regimens. Gemcitabine, ifosfamide and cisplatin (GIP) and gemcitabine, ifosfamide and vinorelbine (GIN) evidenced very interesting results in phase II first-line studies, with a RR of 54% and 52% and a median overall survival (OS) of 12 and 11 months, respectively, with acceptable toxicity profiles (Boni et al, 2000; Baldini et al, 2001). The results of these studies suggested further investigations within prospective randomised study assessing the role of these triplets, with or without platinum. Considering this background, a randomised 2 × 2 factorial phase-II trial addressing two questions: (1) the role of replacing cisplatin (P) with a non-platinum agent, vinorelbine (N), and (2) the role of adding a third agent, ifosfamide (I), in a chemotherapy doublet based on gemcitabine (G) was performed. Here, the results of this multicenter Italian trial are reported.

PATIENTS AND METHODS

Study population

Patients with histologically or cytologically confirmed locally advanced stage IIIB (supra-clavicular node and/or malignant plural effusion) or metastatic stage IV (according sixth TNM classification) NSCLC were eligible for the study. Patients were required to be chemotherapy-naïve for advanced disease. Eligibility criteria included: age ≥18 years, ECOG performance status (PS) ≤2, adequate haematological, hepatic and renal function. Patients with active infection, severe co-morbidity and a history of previous or concomitant neoplasm, other than epithelial tumours of the skin or in situ carcinoma of the uterine cervix, were ineligible.

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the ethics committee of each participating institution and written informed consent was obtained from each patient before inclusion.

Study design and treatment plan

This was a randomised factorial study with the following two primary aims: (1) to compare the effectiveness of two different treatment strategies, one containing cisplatin and one containing vinorelbine instead of cisplatin; (2) to compare the effectiveness of two different treatment strategies, one with two and one with three drugs for the addition of ifosfamide, both in terms of OS.

The factorial design was chosen to improve study efficiency, assuming no interaction between the two factors under investigation.

After stratification by centre, eligible patients were randomly assigned to one of four treatment arms in a 1:1:1:1 ratio: gemcitabine–cisplatin (GP), gemcitabine–vinorelbine (GN), GIP and GIN. Random assignment was centrally performed by fax at the Trial Unit of the National Institute for Cancer Research of Genova with the use of permuted blocks of variable size.

The GP regimen consisted of gemcitabine 1250 mg m⁻² on days 1 and 8 and cisplatin 80 mg m⁻² (infused with hydration) on day 1 every 21 days. The GN regimen consisted of gemcitabine 1250 mg m⁻² on days 1 and 8 and vinorelbine 25 mg m⁻² on days 1 and 8 and every 21 days. The GIP regimen consisted of gemcitabine 1000 mg m⁻² on days 1 and 8, ifosfamide 2 g m⁻² (with mesna total dose of 1200 mg administered as an i.v. bolus immediately before ifosfamide infusion and after 4 and 8 h) on day 1 and cisplatin 80 mg m⁻² (infused with hydration) on day 1 every 21 days. The GIN regimen consisted of gemcitabine 1000 mg m⁻² on days 1 and 8, ifosfamide 3 g m⁻² (with mesna total dose of 1600 mg administered as an i.v. bolus immediately before ifosfamide infusion and after 4 and 8 h) on day 1 and vinorelbine 25 mg m⁻² on days 1 and 8 every 21 days.

Clinical examination was performed before every cycle and 21 days from the end of therapy. Complete blood cell count was performed on day 1 and between days 12 and 14.

Serum liver and renal functions were measured before each cycle of chemotherapy and at the end of the treatment. Dose reductions of single drugs and delay of each cycle were applied according to standard criteria defined by protocol schedules. Primary prophylaxis with G-CSF was not allowed. The treatment was given for a maximum of six cycles unless there were disease progression, unacceptable toxicity or withdrawal of the consent.

Statistical analyses

The primary end point was OS. Secondary end points included characterisation of toxicities, objective RR and progression-free survival (PFS). The study was designed to detect a 25% relative reduction of the mortality hazard, in both planned comparisons (N-based vs P-based regimens and three-drug vs two-drug regimens). We aimed to enrol enough patients to yield the occurrence of 385 deaths, which would give a statistical power of 80% to reject the null hypothesis of no significant difference in the OS time in the two planned comparisons, assuming a hazard ratio (HR) of 0.75, a significance level of a two-sided log-rank test fixed at 5%, an accrual rate equal to 230 patients per year and a minimum follow-up duration of 2 years. No adjustment for multiple comparisons was made.

Overall survival was measured from the date of randomisation to the date of death from any cause. Progression-free survival was measured from the date of randomisation to the first date of disease progression or of death from any cause. In both OS and PFS analyses, observation times were censored at the limit date of 30 September 2009 for patients in whom no event occurred.

Objective response (complete and partial response) was evaluated according to RECIST criteria (version 1.0) (Therasse et al, 2000). Response was assessed after three and six courses with a CT scan. The best overall response is the best response recorded from the start of treatment until disease progression. Patients who received at least one dose of chemotherapy were evaluable for response; any patient who died early, had early suspension of chemotherapy because of any cause or was not evaluated after randomisation was considered non-responder.

Toxicity grading, based on NCI–CTC toxicity criteria (version 2.0, National Cancer Institute of Canada Common Toxicity Criteria, Kingston, ON, Canada), was evaluated weekly. All efficacy analyses were based on the intention-to-treat (ITT) principle. Safety was analysed on all subjects receiving at least one dose of study drugs, according to treatment actually received (safety population).

Median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method. Non-parametric estimates of the survivor functions and hazard
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One patient was assigned to the GP arm but received GN treatment. This patient was included in the GN arm for the safety analysis. GP, gemcitabine–cisplatin; GN, gemcitabine–vinorelbine; GIP, gemcitabine–ifosfamide–cisplatin; GIN, gemcitabine–ifosfamide–vinorelbine.

Patient characteristics

As shown in Table 1, patient characteristics for ITT population at baseline were well balanced between the two groups in both comparisons. The median age of patients was 63 years (range of 29–79). Most patients in all arms were male and had an ECOG PS of 0. In all, 80% of patients in all treatment groups had stage IV or recurrent disease and 27% had squamous histology. Supplementary Table S1 reported baseline patient and tumour characteristics by allocated treatment arm.

Therapy administration and toxicity

The mean and median number of treatment cycles administered were 4.45 and 5 (range 1–6), respectively, in patients treated with GP and GIP and 4.19 and 4 (range 1–6), respectively, for those who received GN and GIN. In the second comparison, the mean and median were 4.37 and 5 (range 1–6), respectively, for patients treated with doublets and 4.27 and 4.5 (range 1–6), respectively, for patients treated with triplets.

Grade 3 and 4 haematologic and non-haematologic toxicities exceeding 5% of the treated patients are reported in Table 2. Haematological toxicity consisted mainly in grade 3–4 anaemia (14% vs 5%; \( P = 0.001 \)), leucopenia (33% vs 23%; \( P = 0.025 \)) and thrombocytopenia (32% vs 4%; \( P < 0.001 \)), significantly more frequent in P-containing vs N-containing regimens. Also febrile neutropenia was significantly more frequent in patients treated with P-containing vs N-containing regimens (3% vs 0.5%; \( P = 0.044 \)). The triplets were more frequently responsible of grade 3–4 leucopenia (35% vs 22%; \( P = 0.003 \)) than doublets.

Concerning non-haematological toxicity, grade 3–4 nausea-vomiting (12% vs 4%; \( P = 0.004 \)) was significantly increased in

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**Results**

Figure 1 summarises patient disposition in the trial. From October 2001 to July 2006, a total of 433 stage IIIB–IV NSCLC patients were enrolled and randomly assigned to one of the four treatment regimens: GP (\( n = 106 \)), GN (\( n = 106 \)), GIP (\( n = 110 \)) and GIN (\( n = 111 \)), at 15 participating Italian centres. Therefore, 216 patients were expected to receive P-based therapy (GP and GIP) and 217 N-based regimen (GN and GIN), whereas 212 patients were expected to be treated with a doublets (GP and GN) and 221 with a triplets (GIP and GIN). Of these 433 patients, 16 (3.7%) did not receive any study therapy; thus, 417 patients are included in the safety analysis population. Six (1.4%) out of 433 patients with non-measurable disease at randomisation were excluded from the analysis of best overall response.
P-containing regimens compared with N-therapy; no other statistically significant differences in toxicity were observed in both comparisons (Table 2).

Supplementary Table S2 reported grade 3 and 4 haematologic and non-haematologic toxicities exceeding 5% of the treated patients by allocated treatment arm.

### Efficacy

Primary efficacy outcomes by two comparisons are summarised in Table 3. Supplementary Table S3 reported response and survival outcomes by allocated treatment arm. Median follow-up was 66.4 months (interquartile range: 49.7–67.5). A total of 29 patients (6.7%) were lost to follow-up. Curves for OS and PFS are summarised in Figure 2 for the two comparisons.

Median OS was 10.3 months for all 433 patients. Adjusted median survival was 11.3 months (95% CI: 9.8–12.7) vs 9.7 months (95% CI: 8.7–10.8) favouring P-containing therapies (HR = 1.23; 95% CI: 1.01–1.49; \( P = 0.044 \)) (Figure 2A). Adjusted median survival was 10.4 months (95% CI: 9.4–12.2) and 10.3 months (95% CI: 9.2–11.8) for doublets and triplets, respectively (HR = 1.03; 95% CI: 0.85–1.25; \( P = 0.781 \)) (Figure 2B). There was no statistically significant interaction between the trial arms (\( P = 0.781 \)).

Adjusted median PFS was 6.4 months for P-containing regimens (95% CI: 5.3–7.1) and 4.9 months for N-containing therapies (95% CI: 4.4–5.8; HR = 1.26; 95% CI: 1.04–1.53; \( P = 0.020 \)) (Figure 2C). Adjusted median PFS was 5.6 months for doublets (95% CI: 4.7–6.6) and 5.7 months for triplets (95% CI: 4.8–6.7; HR = 0.98; 95% CI: 0.81–1.19; \( P = 0.820 \)) (Figure 2D). No evidence of multiplicative interaction between treatment arms was observed (\( P = 0.773 \)).

Adjustment overall RR (complete and partial responses) were 31% vs 24% for platinum vs non-platinum therapies, respectively (OR = 0.72; 95% CI: 0.47–1.10; \( P = 0.124 \)), and 29% vs 26% for doublets and triplets, respectively (OR = 0.86; 95% CI: 0.56–1.32; \( P = 0.487 \)) (test for interaction between trial arms: \( P = 0.748 \)).

### Additional analyses

Clinical results were retrospectively analysed by patient histology (squamous vs non-squamous tumours). The RR in non-squamous tumours was 0.72 (95% CI: 0.47–1.10) for platinum vs non-platinum therapies, and 0.86 (95% CI: 0.56–1.32) for doublets and triplets, respectively (test for interaction between trial arms: \( P = 0.748 \)).
patients was numerically greater than that achieved in squamous (30% vs 23%; P = 0.151). Median survival was 10.8 months (95% CI: 9.7 – 12.4) and 9.4 months (95% CI: 8.4 – 10.4) for non-squamous and squamous patients, respectively (HR = 1.25; 95% CI: 1.00 – 1.56; P = 0.048). Median PFS was 5.8 months (95% CI: 4.9 – 6.7) and 4.9 months (95% CI: 4.3 – 6.0) for non-squamous and squamous patients, respectively (HR = 1.25; 95% CI: 0.95 – 1.46; P = 0.136).

No evidence of interaction effect between histological subtype and treatment type (P- vs N-containing regimens) was observed on RR, PFS and OS (P = 0.943, 0.923 and 0.542, respectively).

**DISCUSSION**

This prospective, factorial randomised trial is the only single study in advanced NSCLC treatment demonstrating a statistically significant slight superiority in survival of platinum-containing regimens over platinum-free chemotherapy. On the contrary, this trial does not provide evidence of an improved outcome with the addition of a third chemotherapy agent, such as ifosfamide, to a standard doublet.

At the time this trial was designed, the controversy about standard chemotherapy treatment of advanced NSCLC was mainly concentrated on the role of platinum and on the optimal number of agents to be used. Therefore, we designed this study aimed at answering with a single study these two relevant questions. Considering, cisplatin–gemcitabine as one of the most widely used platinum-based doublets for the treatment of advanced NSCLC in EU, the available data about GN combination (Gridelli et al, 2000) and the previous experience of our group with two different triplets (GIP and GIN) (Boni et al, 2000; Baldini et al, 2001), we included these four treatment arms in a 2 x 2 factorial study design.

Results from this trial are largely consistent with the data, which have been subsequently available in the literature about the first-line treatment of NSCLC patients and, also, with International guidelines (Azzoli et al, 2009; D’Addario et al, 2010).

No previous study was successful in demonstrating a statistically significant survival advantage in favour of platinum-based regimens, compared with platinum-free combinations. However, in some studies, a trend towards a higher RR or PFS or OS was observed in patients treated with platinum-based combinations compared with those treated with cisplatin-free regimens (Georgoulias et al, 2001, 2004; Kosmidis et al, 2002; Albereta et al, 2003; Gridelli et al, 2003; Smit et al, 2003; Kubota et al, 2008). D’Addario et al (2005) reported the results of a meta-analysis based on abstracted data from randomised phase II and III studies designed to compare the efficacy and toxicity of platinum-based to non-platinum-based chemotherapy in advanced NSCLC. As in our trial, the platinum-based combinations had a significantly higher 1-year survival rate compared with the non-platinum regimens.

The results of our study concerning this comparison are consistent also with the results of two other meta-analysis of phase III trials comparing third-generation platinum- vs non-platinum-based combinations (Pujol et al, 2006; Rajeswaran et al, 2008). Pujol et al (2006) showed that patients treated with platinum-based doublets had a statistically significant reduction in the risk of death (OR = 0.88, P = 0.044) without an unacceptable increase in toxicity. Moreover, Rajeswaran et al (2008) confirmed that cisplatin-, but not carboplatin-based regimens, are associated with a slight survival advantage at 1-year compared with non-platinum-based doublets.

In our study, the absolute benefit at 1-year turns out to be relatively small, but it becomes more relevant later, as shown in the Kaplan–Meier curve, with a higher percentage of long-term surviving patients in the P-containing arms. This result is reinforced by the high median follow-up time (66.4 months) of our study. This is in keeping with the hypothesis that the added benefit of platinum, albeit quantitatively small, may translate into a long-term higher survival probability.

P-containing regimens showed, moreover, a short-term benefit in PFS, about 2 months in median PFS and 6.8% absolute improvement in 1-year PFS probability, without any statistically
significant difference in RR. This observation might be probably related to the high percentage (22%) of patients not evaluable for response due to the lack of uniform external and blinded radiological response assessment.

One of the most remarkable results of the study was the fairly good tolerability of all the four regimens, with a slightly higher haematological toxicity in P-containing regimens, which were penalised also by a higher incidence of nausea-vomiting.

Also the triplets were well tolerated, even if with significantly more grade 3-4 leucopenia compared with doublets. According to previous results, also in our trial the addition of a third agent to 2-drug regimens was lower than that reported in phase II studies. In addition, the RR observed in this trial was lower than that reported in phase II experience. In addition, the RR observed in this trial observed three-drug regimens under testing in accordance to previous phase II experience. In addition, the RR observed in this trial observed doses of both gemcitabine and ifosfamide were different in the three-drug regimens under testing in accordance to previous phase II experience. In addition, the RR observed in this trial observed with triplets was lower than that reported in phase II studies probably as consequence of less stringent eligibility criteria and radiological response assessment.

Overall, the outcome data obtained in the FAST trial population were good; in particular, a median survival of 10.3 months was observed in the overall population, which compares favourably with that of the more relevant randomised phase III trials performed with different platinum doublets, where the median OS ranged between 7.4 and 9.9 months (Kelly et al, 2001; Scagliotti et al, 2002; Schiller et al, 2002). Moreover, all outcome measures were similar in squamous and non-squamous histology subtypes, suggesting the lack of treatment-histology interactions with the chemotherapy regimens used in this study.

With the limitations of long study duration, this trial confirms that in advanced NSCLC patients with a PS of 0 or 1, a two-drug platinum-based combination, such as cisplatin-gemcitabine, should be preferred as first-line treatment. The results of this trial along with those of platinum vs non-platinum meta-analysis and of carboplatin vs cisplatin meta-analysis, suggest that cisplatin should remain a fundamental ingredient of first-line chemotherapy of advanced NSCLC patients, especially when a long-term survival can be anticipated, such as in fit patients with oligometastatic disease. Non-platinum combinations, however, can remain a reasonable option in patients who have contraindications to platinum therapy or those who are unfit or have very advanced bulky and multimetastatic disease.

On the contrary, our study, in keeping with the results of a meta-analysis, further supports the concept that, at the moment, there is no place for increasing the number of chemotherapy agents beyond two in first-line regimens in the treatment of advanced NSCLC. Perhaps, the use of triplets might deserve further investigation in locally advanced non-metastatic disease where the increased RR associated with this strategy, as seen in some other studies, might lead to an improvement of tumour down-staging and, ultimately, to a better local control with subsequent locoregional therapies.

Although the currently most employed drug combinations for first-line treatment of advanced NSCLC, such as cisplatinum-pemetrexed and carboplatin-paclitaxel-bevacizumab (Sandler et al, 2006; Scagliotti et al, 2008), were not included in this study, we believe that our results can contribute further to the clarification of the optimal chemotherapy management of advanced NSCLC.
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