original article

*Annals of Oncology* 18: 324–330, 2007
doi:10.1093/annonc/mdl396
Published online 27 October 2006

# Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: a phase III randomised trial of the Southern Italy Cooperative Oncology Group (SICOG 0101)

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*Received 18 July 2006; revised 7 September 2006; accepted 14 September 2006*

**Background:** Triplet regimens were occasionally reported to produce a higher response rate (RR) than doublets in locally advanced or metastatic non-small-cell lung cancer (NSCLC). This trial was conducted to assess (i) whether the addition of cisplatin (CDDP) to either gemcitabine (GEM) and vinorelbine (VNR) or GEM and paclitaxel (PTX) significantly prolongs overall survival (OS) and (ii) to compare the toxicity of PTX-containing and VNR-containing combinations.

**Patients and methods:** Stage III or IV NSCLC patients were randomly assigned to (i) GEM 1000 mg/m$^2$ and VNR 25 mg/m$^2$ on days 1 and 8 (GV arm); (ii) GEM 1000 mg/m$^2$ and PTX 125 mg/m$^2$ on days 1 and 8 (GT arm); (iii) GV plus CDDP 50 mg/m$^2$ on days 1 and 8 (PGV arm); and (iv) GT plus CDDP 50 mg/m$^2$ on days 1 and 8 (PGT arm). Treatments were repeated every 3 weeks for a maximum of six cycles.

**Results:** A total of 433 (stage III, 160; stage IV, 273) patients were randomly allocated to the study. RR was 48% [95% confidence interval (CI), 42% to 54%] for triplets and 35% (95% CI, 32% to 38%) for doublets ($P$ = 0.004). Median progression-free survival (6.1 versus 5.5 months, $P$ = 0.706) and median OS (10.7 versus 10.5 months, $P$ = 0.379) were similar. CDDP significantly increased the occurrence of severe neutropenia (35% versus 13%), thrombocytopenia (14% versus 4%), anaemia (9% versus 3%), vomiting (6% versus 0.5%), and diarrhoea (6% versus 2%). Conversely, frequency of severe neutropenia (30% versus 17%) and thrombocytopenia (11% versus 6%) was significantly higher with VNR-containing regimens.

**Conclusions:** Adding CDDP to GV or GT significantly increased RR, but did not prolong the OS of patients. Among doublets, the GT regimen should be preferred in view of its better safety profile.

**Key words:** cisplatin, gemcitabine, non-small-cell lung cancer, paclitaxel, vinorelbine

## introduction

Despite recent advances in cancer management, prognosis for advanced non-small-cell lung cancer (NSCLC) patients remains very poor. In the middle of the 1990s, a cisplatin (CDDP) or carboplatin (CBDCA)-including treatment was established as the standard of care for these patients, because it was demonstrated to produce a small but significant prolongation of overall survival (OS) in comparison with best supportive care alone [1–3], to improve symptoms, and to preserve the quality of life [4, 5].

In more recent years, new drugs such as vinorelbine (VNR), gemcitabine (GEM), paclitaxel (PTX), and docetaxel (DTX)

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showed promising activity when combined with platinum compounds [6–9]. Subsequent randomised trials, comparing the efficacy of these novel doublets, failed to highlight any significant difference in OS among them [10–12], indicating that their choice should be on the basis of toxicity, patient's preference, and cost.

In the same time, we have pursued the hypothesis that a triplet regimen, combining two new agents with CDDP, could improve the OS of patients, provided that they were aged ≤70 years and in a good performance status (PS). Two regimens, i.e. CDDP, GEM, and VNR (PGV), and CDDP, GEM and PTX (PGT) were demonstrated to be safe and active in patients with such characteristics [13, 14]. Therefore, we randomly compared both these triplets with CDDP-including doublets (CDDP and VNR, and CDDP and PTX regimens) [15, 16]. Median OSs produced by either triplet were similar, and were significantly longer than those obtained by CDDP and GEM, or CDDP and PTX. Other investigators have explored such hypothesis, reporting conflicting results [17–22].

More recently, CDDP-free doublets, such as GEM and VNR, GEM and PTX, or GEM and DTX, have been employed as front-line treatment in NSCLC patients. Randomized trials showed that CDDP-free doublets were as effective as CDDP-including doublets [12, 23–26]. These CDDP-free regimens seem appealing because they not only permit spare CDDP toxicity but may also be easily delivered in a shorter time and in an outpatient setting.

With these considerations in mind, we planned this randomised trial, with the aim of assessing whether PGV and PGT triplets were more effective than the corresponding CDDP-free doublets (GEM and VNR, and GEM and PTX), and to compare the toxicity profile of PTX-including (PGT and GT) and VNR-including (PGV and GV) combinations.

## patients and methods

### patient selection

The patients eligible for this study were those with histologically or cytologically proven NSCLC in stage IIIA not amenable to surgical treatment for medical contraindications, stage IIIB, or IV. Other inclusion criteria were the following: presence of at least one measurable lesion, age ≤70 years, Eastern Cooperative Oncology Group PS of 1 or less, adequate bone marrow reserve (i.e. absolute neutrophil count $\geq 2 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and haemoglobin level ≥100 g/l), normal liver function, creatinine clearance ≥60 ml/min, no prior chemotherapy, and a life expectancy ≥12 weeks. Patients already exposed to thoracic radiotherapy should have at least one measurable lesion outside the irradiated field. Exclusion criteria were as follows: presence of symptomatic central nervous system (CNS) metastases (previously treated and asymptomatic CNS metastases were allowed), presence of severe cardiac arrhythmia, second- or third-degree heart block, or acute myocardial infarction within 4 months before study entry, previous or concurrent malignancy. The Independent Ethics Committee of the National Tumor Institute of Naples approved the study protocol, and each patient gave written informed consent before being randomly assigned.

### baseline and follow-up assessment

Pre-treatment evaluation included the following: complete history and physical examination, electrocardiogram, chest X-ray, fiberoptic broncoscopy, and chest and upper abdomen computed tomography (CT) scan. Radionuclide bone scan and brain CT scan were also performed in symptomatic patients. Laboratory investigation included the following: complete blood cell count with WBC differential and platelet count, and full biochemistry profile. After discontinuation of chemotherapy, physical examination and laboratory tests were performed monthly, while diagnostic procedures to assess disease status were repeated every 2 months or earlier, if required, by clinical conditions.

### treatment

Patients were stratified according to centre and stage (III versus IV), and randomly allocated to one of four arms: (i) GEM 1000 mg/m$^2$ i.v. for a period of 30 min and VNR 25 mg/m$^2$ i.v. for a period of 15 min, on days 1 and 8 (GV regimen); (ii) GEM 1000 mg/m$^2$ (as above) and PTX 125 mg/m$^2$ i.v. for a period of 60 min, on days 1 and 8 (GT regimen); (iii) CDDP 50 mg/m$^2$ i.v. for a period of 60 min on days 1 and 8 added to GV (PGV regimen); and (iv) CDDP 50 mg/m$^2$ (as above) on days 1 and 8 added to GT (PGT regimen). In all arms, cycles were repeated every 3 weeks. A short-term i.v. hydration was performed before and after CDDP delivery. Pre-medication for PTX consisted of dexamethasone, diphenydramine, and ranitidine, all delivered 30–60 min before PTX infusion. Antiemetic prophylaxis consisted in all arms of hydroxytryptamine-3-receptor antagonists.

In all arms, full doses of chemotherapy were given if neutrophil count was $\geq 2.0 \times 10^9$/l, and platelet count $\geq 100 \times 10^9$/l. If a grade 1 neutropenia or thrombocytopenia occurred on the first day, treatment was delayed for 1 week, and if a grade 1 toxicity persisted after the 1-week delay, GEM, VNR, and PTX doses were reduced by 25%. If a grade 1 neutropenia or thrombocytopenia occurred on the eighth day of treatment, a 25% dose reduction was applied. In the presence of grade ≥2 neutropenia or thrombocytopenia, therapy was always omitted. Drug doses were also reduced by 25% if a grade 4 neutropenia and/or thrombocytopenia, or a grade ≥3 non-haematologic toxicity had occurred in the previous course. CDDP was reduced by 50% for creatinine serum concentration >1.4 mg/dl, and omitted for level >2.0 mg/dl. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not allowed. Therapeutic G-CSF was delivered only in the presence of neutropenic fever.

Three cycles were planned before the assessment of tumour response, unless treatment was discontinued earlier for toxicity or disease progression, and responding patients received a maximum of three further cycles. Thoracic radiotherapy could be delivered after chemotherapy in patients with intra-thoracic disease. Second-line chemotherapy was unplanned, and it was delivered according to individual centre policy.

### evaluation of toxicity

Toxic effects were graded according to World Health Organisation (WHO) criteria [28], and the worst score registered during treatment by each patient was recorded. Haematologic toxicity was assessed performing a blood cell count and WBC differential weekly. Non-haematologic toxicity was assessed at the time of recycling.

### evaluation of activity

Responses were classified according to WHO criteria [28]. An early treatment withdrawn for whatever reason was considered a treatment failure, and included in this analysis. Therefore, patients not formally assessed for response after three cycles were also included in the activity analysis according to an intention-to-treat principle. Duration of response was calculated from the date of initial therapy to the date of documented tumour progression, clinical deterioration, or death.

### aims of the study

The aims of this trial were as follows: (i) to compare the OS produced by triplets and doublets and (ii) to compare the toxicity of PTX-including and VNR-including regimens. Secondary end points were the following: response rate (RR), duration of responses, and progression-free survival (PFS).

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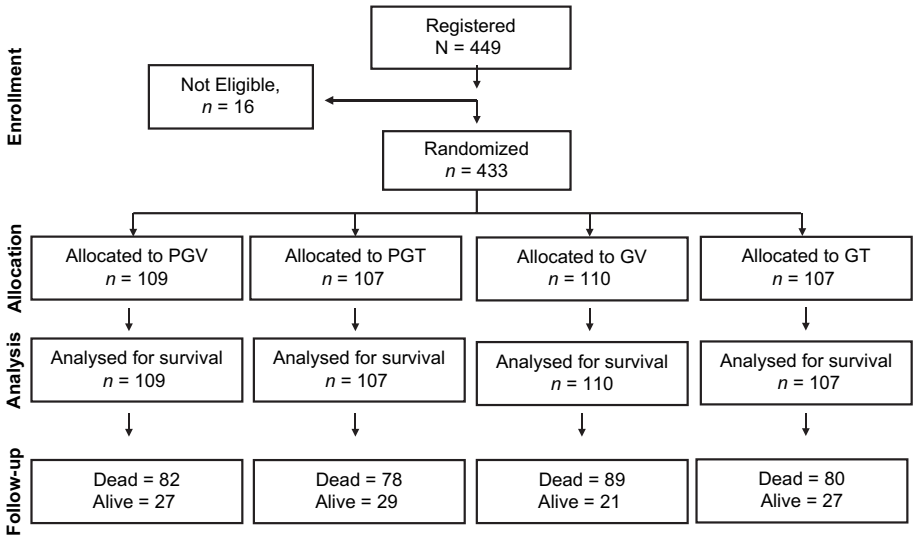


**Figure 1.** CONSORT (Consolidation of Standards for Reporting Trials) flow chart of Southern Italy Cooperative Oncology Group (SICOG 0101) study.

### design of the study and sample size

A factorial design, which allowed two independent statistical comparisons, was adopted. OS data of patients treated with triplets were pooled and compared with the pooled data of patients treated with doublets. Three-hundred and thirty events had a 90% power to demonstrate, with an alpha error <0.05, a 30% reduction of the hazard of death. Therefore, a total accrual of 400 patients was planned. Severe toxicity of VNR-including regimens was pooled and compared with the pooled toxicity of PTX-including regimens.

### statistical

Analysis of survival was performed according to intent-to-treat. OS was calculated from the date of randomisation to the date of death or last follow-up. PFS was calculated from the date of randomisation to the date of documented tumour progression, death, or last follow-up. PFS and OS curves were plotted according to Kaplan and Meier [29], and compared using a two-sided log-rank test [30]. A Cox test for interaction was planned to exclude that the combination of CDDP with either GV or GT could have a different effect on OS. Baseline demographic and clinical factors were assessed by multivariate analysis for an independent effect on time-to-event results [31]. Proportions were compared using the Fisher's exact test [32]. Median values were compared using the rank sum test. Statistical analyses were made using the SPSS statistical package (version 12.0).

## results

### patient characteristics

From April 2001 to December 2005, 449 consecutive patients were registered. Sixteen patients, however, were not eligible (diagnosis of small-cell lung cancer, two patients; lack of baseline characteristics, three patients; and withdraw of consent, 11 patients). Therefore, 433 patients (216 in the triplet arms and 217 in the doublet arms) were randomly allocated to the study (Figure 1). Baseline demographic and clinical characteristics were evenly distributed in the two groups (Table 1). Few patients had previously received primary surgery (7%) or radiotherapy (4%). Squamous cell carcinoma accounted for 40% of all histologies, followed by adenocarcinoma (36%). Twenty-four percent of patients were in PS of 0, and 76% in PS of 1. Sixty-three percent of patients were in stage IV, and 32% had more than one metastatic site of disease.

### delivered cycles and dose intensity

A total of 1760 cycles (925 triplets and 835 doublets) were delivered. Median number of delivered cycles per patient was four (range 1–6) for triplets, and three (range 1–6) for doublets. In the two groups, five (three versus two) patients underwent primary surgery after three cycles; 13 (nine versus four) patients were withdrawn for toxicity, and 23 (13 versus 10) patients for patient's refusal.

To avoid the bias due to different numbers of delivered cycles, actually delivered dose intensity (DI) was calculated and compared over the first three cycles (Table 2). A significantly lower median DI of GEM was delivered with triplets (525 mg/m$^2$/week) as compared with doublets (609 mg/m$^2$/week) ($P = 0.001$). Median DIs of VNR (13 mg/m$^2$/week versus 14 mg/m$^2$/week) and of PTX (65 versus 73 mg/m$^2$/week) were also slightly but significantly lowered ($P = 0.001$) by the addition of CDDP, which was delivered in both triplets with a median DI of 26 mg/m$^2$/week.

### post-study treatment

Forty-seven (22%) patients in the triplet arms and 42 (19%) patients in the doublet arms underwent palliative thoracic radiotherapy. Second-line chemotherapy was delivered to 25 (12%) and 35 (16%) patients, respectively.

### activity

Table 3 reports the best responses achieved according to each treatment. On the whole, triplets produced a significantly greater RR [48%; 95% confidence interval (CI) 42% to 54%] than doublets (35%; 95% CI 32% to 38%) ($P = 0.004$). Conversely, the proportion of stable disease was about two times greater with doublets. A similar number (35 versus 38) of patients were not assessed for response in the triplet and doublet group because of refusal (nine versus four), toxicity (13 versus

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**Table 1.** Patient characteristics according to the four arms of treatment

| Characteristics | CDDP-including triplets | | | | CDDP-free doublets | | | |
|---|---|---|---|---|---|---|---|---|
| | PGV | PGT | Total | | GV | GT | Total | |
| | No. | No. | No. | % | No. | No. | No. | % |
| Eligible patients | 109 | 107 | 216 | 100 | 110 | 107 | 217 | 100 |
| Males | 93 | 88 | 181 | 84 | 98 | 100 | 198 | 91 |
| Females | 16 | 19 | 35 | 16 | 12 | 7 | 19 | 9 |
| Median age | | 60 (32–70) | | | | 63 (33–70) | | |
| Histology | | | | | | | | |
| Squamous carcinoma | 49 | 35 | 84 | 39 | 49 | 40 | 89 | 41 |
| Adenocarcinoma | 37 | 44 | 81 | 38 | 38 | 40 | 78 | 36 |
| Large cell | 8 | 9 | 17 | 8 | 12 | 15 | 27 | 12 |
| Not specified | 15 | 19 | 33 | 15 | 11 | 12 | 23 | 11 |
| Previous surgery | 9 | 8 | 17 | 8 | 9 | 6 | 15 | 6 |
| Previous radiotherapy | 6 | 4 | 10 | 5 | 4 | 3 | 7 | 3 |
| ECOG PS | | | | | | | | |
| 0 | 26 | 27 | 53 | 25 | 32 | 18 | 50 | 23 |
| 1 | 83 | 80 | 163 | 75 | 78 | 89 | 167 | 77 |
| Weight loss >5% Stage | 25 | 23 | 48 | 22 | 31 | 30 | 61 | 28 |
| IIIA | 6 | 3 | 9 | 4 | 5 | 6 | 11 | 5 |
| IIIB | 44 | 27 | 71 | 33 | 33 | 36 | 69 | 32 |
| IV | 59 | 77 | 136 | 63 | 72 | 65 | 137 | 63 |
| >1 metastatic site | 34 | 36 | 70 | 32 | 38 | 31 | 69 | 32 |
| Brain metastases | 4 | 7 | 11 | 5 | 11 | 4 | 15 | 7 |

CDDP, cisplatin; PGV, cisplatin, gemcitabine, vinorelbine; PGT, cisplatin, gemcitabine, paclitaxel; GV, gemcitabine, vinorelbine; GT, gemcitabine, paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status.

10), or early deterioration of clinical conditions (13 versus 24). RR of triplets was greater in stage III (57% versus 37%, $P = 0.007$) than in stage IV patients (42% versus 33%, $P = 0.084$). An insignificantly greater RR was reported with PTX-containing (44%; CI 37% to 51%) as opposed to VNR-containing regimens (38%; CI 35% to 41%) ($P = 0.139$). Duration of responses was exactly the same for the triplet and doublet arms, i.e. 8.8 (95% CI 6.8 to 10.8) months.

### progression-free survival

Median (95% CI) PFS was 6.1 (5.1 to 7.1) months for triplet arms and 5.5 (4.5 to 6.5) months for doublet arms ($P = 0.706$) (Figure 2). For patients in stage IV, median PFS was 6.3 (5.4–7.2) months for those treated with triplets as opposed to 4.8 (3.2–6.0) months for those treated with doublets. Number of metastatic sites ($P = 0.001$) and presence of symptoms ($P = 0.002$) were the only factors independently affecting PFS at multivariate analysis.

### overall survival

After a median follow-up of 36 (range 6–62) months, 329 (76%) patients had died. Figure 3 depicts the OS curves of patients treated with triplets or doublets. Eighteen patients (eight patients in triplet arms and 10 patients in doublet arms) died within 1 month from initial treatment. Median (95% CI) OS was 10.7 (9.2–12.2) months for triplets, and 10.5 (8.9–12.1) months for doublets. Corresponding 1- and 2-year probability of survival were 44% and 20% versus 40% and 15% ($P = 0.379$).

According to stage, median (95% CI) OS for patients in stage III was 11.0 (8.7–13.3) months for those treated with triplets and 10.7 (9.7–11.7) for those treated with doublets. These values for patients in stage IV were 9.6 (7.6–11.6) and 9.2 (6.3 to 12.2) months, respectively, with a 2-year probability of survival of 18% versus 15%.

A *post-hoc* evaluation indicated that PGV-treated patients had a longer OS in comparison GV-treated patients (median 10.2 versus 8.8 months), whereas PGT- and GT-treated patients had a similar outcome (median 11.2 versus 11.1 months). In the multivariate analysis, only the presence of symptoms ($P = 0.001$), and the number of metastatic sites ($P = 0.001$) independently affected the OS.

### toxicity

Occurrence of grade ≥3 toxicity over the first three cycles is reported in Table 4. Severe neutropenia (35% versus 13%, $P < 0.0001$), thrombocytopenia (14% versus 4%, $P < 0.0001$), and anaemia (9% versus 3%, $P = 0.006$) were significantly worse with the triplets. Frequency of febrile neutropenia, however, was similar (5% versus 3%). No patient showed bleeding, and platelet transfusions were never required. Addition of CDDP produced a significantly greater occurrence of severe vomiting (6% versus 0.5%, $P = 0.008$) and diarrhoea (6% versus 2%, $P = 0.022$). No other significant differences were seen between triplets and doublets.

On the other hand, occurrence of grade ≥3 neutropenia (30% versus 17%, $P = 0.001$) and thrombocytopenia (11% versus 6%, $P = 0.036$) was significantly greater with the VNR-containing than with the PTX-containing regimens. Conversely, severe non-haematologic toxic effects were absolutely comparable in the two groups (Table 5).

## discussion

Southern Italy Cooperative Oncology Group (SICOG 0101) trial was designed to assess whether CDDP-including triplets could obtain a significant prolongation of OS in comparison with their corresponding CDDP-free doublets. Results of this trial, although reporting a significantly greater RR for triplets, failed to demonstrate a benefit on OS. On the contrary, patients treated with CDDP-free doublets had an OS almost identical with that of patients enrolled in the triplet arms.

To explain these results we may infer that the increased RR we have obtained combining CDDP with two highly effective doublets was too small, namely in metastatic patients, to significantly affect the PFS and OS of the whole series. Indeed, the odds ratio for response was lower than that observed in our previous experience, because a greater proportion of patients in the present trial responded to CDDP-free doublets, in contrast with the RR achieved with CDDP-based doublets in our previous studies [15, 16].

This observation seems in agreement with the findings of some recent randomised trials assessing the combination of a third drug to doublets, reporting with triplets either a similar activity or an incremental activity that was not enough to impact

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**Table 2.** Median actually delivered (mg/m$^2$/week) and relative dose intensity of cytotoxic drugs over the first three cycles according to the four arms of treatment

| Drugs | Dose intensity | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CDDP-including triplets | | | | CDDP-free doublets | | | |
| | PGV | | PGT | | GV | | GT | |
| | mg/m$^2$/week | RDI (%) | mg/m$^2$/week | RDI (%) | mg/m$^2$/week | RDI (%) | mg/m$^2$/week | RDI (%) |
| Gemcitabine | 545 | 81 | 514 | 77 | 610 | 92 | 575 | 86 |
| Cisplatin | 27 | 82 | 25 | 76 | 0 | 0 | 0 | 0 |
| Paclitaxel | 0 | 0 | 62 | 75 | 0 | 0 | 75 | 90 |
| Vinorelbine | 13 | 76 | 0 | 0 | 15 | 88 | 0 | 0 |

CDDP, cisplatin; RDI, relative dose intensity; PGV, cisplatin, gemcitabine, vinorelbine; PGT, cisplatin, gemcitabine, paclitaxel; GV, gemcitabine, vinorelbine; GT, gemcitabine, paclitaxel.

**Table 3.** Activity reported according to arms of treatment

| Responses | CDDP-including triplets (N = 216) | | | | CDDP-free doublets (N = 217) | | | |
|---|---|---|---|---|---|---|---|---|
| | PGV | PGT | Total | % | GV | GT | Total | % |
| Complete | 6 | 3 | 9 | 4 | 3 | 2 | 5 | 2 |
| Partial | 44 | 50 | 94 | 44 | 31 | 39 | 70 | 32 |
| Stable | 16 | 18 | 34 | 16 | 36 | 30 | 66 | 30 |
| Progression | 28 | 16 | 44 | 20 | 22 | 16 | 38 | 18 |
| Not assessed | 15 | 20 | 35 | 16 | 18 | 20 | 38 | 18 |
| RR (95% CI) | 48% (42%–54%) | | | | 35% (32%–38%) | | | |

CDDP, cisplatin; PGV, cisplatin, gemcitabine, vinorelbine; PGT, cisplatin, gemcitabine, paclitaxel; GV, gemcitabine, vinorelbine; GT, gemcitabine, paclitaxel; RR, response rate; CI, confidence interval.

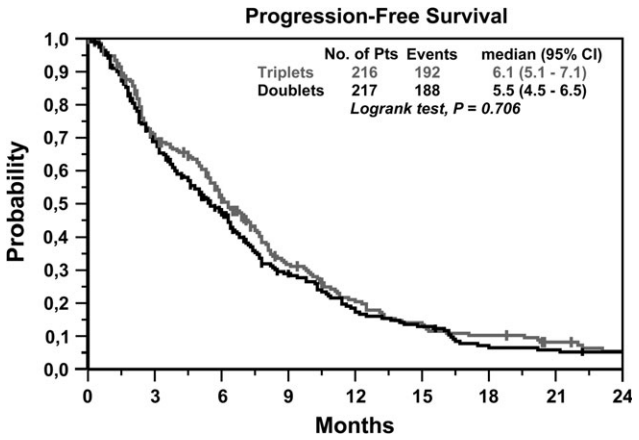


**Figure 2.** Progression-free survival curves: cisplatin (CDDP)-including triplets versus CDDP-free doublets.

on the OS. Indeed, adding ifosfamide to CDDP and VNR was reported to improve neither the RR (36% versus 35%) nor the OS (8.2 versus 10.0 months), but it should be noted that in that study, the planned and actually delivered DI of VNR was reduced in the triplet (14.6 mg/m$^2$/week) as compared with the doublet (17.9 mg/m$^2$/week) combination [18]. Similarly, no difference neither in RR (42% versus 41%) nor in OS (8.2 versus 9.3 months) was seen when adding VNR to CDDP and GEM. Also in this trial, a lower DI of GEM was planned and delivered in the triplet (888 versus 1168 mg/m$^2$/week) [19]. At this proposal, we would remember that in our study, actually delivered DI of GEM was meaningfully decreased (by about 15%) by adding CDDP in the triplet combinations.

On the other hand, the combination of GEM with CDDP and VNR was reported to obtain a RR two times greater than that of the doublet (28% versus 13%). The proportion of responding patients in the triplet arm, however, was still too small a fraction of the treated series to impact significantly on the median OS, which resulted to be 35.9 versus 32.4 weeks [21]. By contrast, when GEM was added to CBDCA and PTX, a significantly longer OS (10.8 versus 8.3 months) was reported and indeed about half the treated patients in that trial achieved a response (44% versus 20%) with the triplet combination [22].

The relationship between a greater treatment activity and a longer OS of patients has recently been highlighted by a literature-based meta-analysis, in which the benefit of doublets versus single-agent treatments and of triplets versus doublets was assessed. Pooled comparison of two-drug versus single-agent treatments showed a 13% absolute increase of RR (odds ratio, 1.58), which was associated with a significant improvement of median and 1-year survival, in favour of doublets. Conversely, adding a third drug to doublets resulted in a smaller increase of activity (8% absolute difference; odds ratio, 1.34), which did not translate in a survival prolongation [23].

Another explanation for our results may be that CDDP added to doublets, while increasing the killing of sensitive cells, did not prevent the emergence of resistant tumour clones, which ultimately affected the OS of patients, especially when no salvage therapy was delivered. At this proposal, given that this trial was designed several years ago, we would remark that no second-line therapy, neither with cytotoxic nor with biologic drugs, was planned, and very few patients actually received a salvage treatment.

Considering the efficacy of CDDP-free doublets, we may argue that a platinum-based regimen should be no longer considered as the only standard of treatment of metastatic NSCLC. Indeed, the median OS of 9.2 months for stage IV patients obtained with our doublets compared well with that reported with platinum-including [10–12] as well as with similar platinum-free doublets [12, 24–27]. A recent meta-analysis on this issue, although showing that platinum-based therapies were associated with a 5% increase of 1-year survival,

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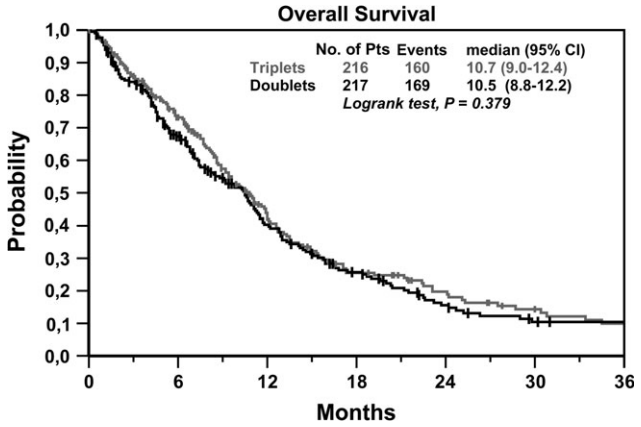


**Figure 3.** Overall survival curves: cisplatin (CDDP)-including triplets versus CDDP-free doublets.

**Table 4.** Occurrence of grade ≥3 toxicity over the first three cycles: the *P* values result from the Fisher's test comparing CDDP-including triplets versus CDDP-free doublets

| Toxicity | CDDP-including triplets (N = 216) | | | | CDDP-free doublets (N = 217) | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | PGV | PGT | Total | | GV | GT | Total | | |
| | No. | No. | No. | % | No. | No. | No. | % | |
| Neutropenia | 46 | 29 | 75 | 35 | 20 | 8 | 28 | 13 | <0.0001 |
| Febrile neutropenia | 5 | 5 | 10 | 5 | 3 | 3 | 6 | 3 | 0.220 |
| Anaemia | 11 | 8 | 19 | 9 | 4 | 2 | 6 | 3 | 0.006 |
| Thrombocytopenia | 20 | 10 | 30 | 14 | 5 | 3 | 8 | 4 | <0.0001 |
| Vomiting | 5 | 6 | 13 | 6 | 1 | 0 | 1 | 0.5 | 0.008 |
| Diarrhoea | 4 | 9 | 13 | 6 | 2 | 2 | 4 | 2 | 0.022 |
| Fatigue | 4 | 5 | 9 | 4 | 3 | 1 | 4 | 2 | 0.128 |
| Stomatitis | 1 | 3 | 4 | 2 | 0 | 3 | 3 | 1 | 0.497 |
| Neuropathy | 1 | 0 | 1 | 0.5 | 0 | 2 | 2 | 1 | 0.5 |
| Hepatic | 0 | 1 | 1 | 0.5 | 2 | 1 | 3 | 1 | 0.312 |
| Renal | 0 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0.248 |
| Constipation | 1 | 1 | 2 | 1 | 2 | 2 | 4 | 2 | 0.345 |
| Skin | 1 | 1 | 2 | 1 | 2 | 2 | 4 | 2 | 0.345 |

CDDP, cisplatin; PGV, cisplatin, gemcitabine, vinorelbine; PGT, cisplatin, gemcitabine, paclitaxel; GV, gemcitabine, vinorelbine; GT, gemcitabine, paclitaxel.

was unable to demonstrate a statistically significant OS prolongation when platinum-based regimens were compared with 'third-generation' platinum-free combinations [33].

As regards to safety, we observed that neutropenia was strongly reduced with PTX-containing treatments. Therefore, although neutropenic fever or infections were infrequent with both type of combinations, we believe that a PTX-containing regimen should be preferred to a VNR-containing regimen. Tolerability and efficacy of GT regimen in this study was likely enhanced by limiting the number of delivered cycles, and by splitting PTX in two administrations delivered with GEM, so at best exploiting any positive pharmacokinetic and pharmacodynamic interaction between them [34]. On the other hand, we have already demonstrated the feasibility and efficacy of the GT regimen in elderly NSCLC patients in preserved PS [35].

**Table 5.** Occurrence of grade ≥3 toxicity over the first three cycles: the P values result from the Fisher's test comparing PTX-containing versus VNR-containing regimens

| Toxicity | PTX-containing regimens (N = 214) | | | | VNR-containing regimens (N = 219) | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | PGT | GT | Total | | PGV | GV | Total | | |
| | No. | No. | No. | % | No. | No. | No. | % | |
| Neutropenia | 29 | 8 | 37 | 17 | 46 | 20 | 66 | 30 | 0.001 |
| Febrile neutropenia | 5 | 3 | 8 | 4 | 5 | 3 | 8 | 4 | 0.581 |
| Anaemia | 8 | 2 | 10 | 5 | 11 | 4 | 15 | 7 | 0.223 |
| Thrombocytopenia | 10 | 3 | 13 | 6 | 20 | 5 | 25 | 11 | 0.036 |
| Vomiting | 6 | 0 | 6 | 3 | 5 | 1 | 6 | 3 | 0.598 |
| Diarrhoea | 9 | 2 | 11 | 5 | 4 | 2 | 6 | 3 | 0.149 |
| Fatigue | 5 | 1 | 6 | 3 | 4 | 3 | 7 | 3 | 0.517 |
| Stomatitis | 3 | 3 | 6 | 3 | 1 | 0 | 1 | 0.5 | 0.057 |
| Neuropathy | 0 | 2 | 2 | 1 | 1 | 0 | 1 | 0.5 | 0.491 |
| Hepatic | 1 | 1 | 2 | 1 | 0 | 2 | 2 | 1 | 0.679 |
| Renal | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0.244 |
| Constipation | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0.5 | 0.506 |
| Skin | 1 | 2 | 3 | 1 | 1 | 2 | 3 | 1 | 0.646 |

PTX, paclitaxel; VNR, vinorelbine; PGV, cisplatin, gemcitabine, vinorelbine; PGT, cisplatin, gemcitabine, paclitaxel; GV, gemcitabine, vinorelbine; GT, gemcitabine, paclitaxel.

In conclusion, CDDP-including triplets were highly active, but they did not improve the OS in comparison with their CDDP-free counterparts. Therefore, a doublet of cytotoxic drugs remains the standard treatment of metastatic NSCLC patients. The GT regimen, in view of its efficacy and tolerability, should be considered as a therapeutic option for these patients.

## acknowledgements

This trial was partially supported by a grant from the Italian National Research Council, Oncology Special Project SP/5, 2001. We wish to thank Marina Licenziato for her excellent data management and Liliana Gallifuoco for her invaluable secretarial assistance. Results of this trial were presented in part at the 2006 American Society of Clinical Oncology Annual Meeting, 2–6 June, Atlanta, GA.

We acknowledge the participation in this trial of the following investigators (and institutions) of the Southern Italy Cooperative Oncology Group: Pasquale Comella, Giuseppe Frasci, Antonio Avallone (Division of Medical Oncology A, National Tumour Institute, Naples); Gianfranco Filippelli, Virginia Olivito, Gianluca Dima (City Hospital, Paola); Giuseppe De Cataldis, Pietro Carnicelli (Division of Medical Oncology, Da Procida Hospital, Salerno); Bruno Massidda, Maria Teresa Ionta, Efisio Mereu (Chair of Medical Oncology, University Medical School, Cagliari); Luigi Maiorino, Manuela Musicò (Division of Medical Oncology, San Gennaro Hospital, Naples); Carlo Putzu, Antonio Farris (Chair of Medical Oncology, University Medical School, Sassari); Sergio Mancarella (Medical Oncology, City Hospital, Campi Salentino); Sergio Palmeri, Marina Vaglica (Chair of Medical Oncology, University Medical School, Palermo); Riccardo Cioffi, V. Messina (Division of Pneumology, City Hospital,

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Caserta); Mario Roselli, Sabrina Mariotti (Chair of Medical Oncology, Tor Vergata University Medical School, Rome); Franco Buzzi (Medical Oncology, City Hospital, Terni); Valerio Milia (Medical Oncology, City Hospital, Macomer); Antonio Gambardella (Chair of Geriatrics, Second University Medical School, Naples); Maddalena Bianco (Medical Oncology, San Leonardo Hospital, Castellammare); Donato Natale (Medical Oncology, City Hospital, Penne); Massimo Ghiani (Medical Oncology City Hospital, Oristano); Pietro Masullo (Medical Oncology, City Hospital, Vallo della Lucania); Enrico Barbato (Medical Oncology, City Hospital, Aversa); Italy.

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