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Randomized phase II three-arm trial with three platinum-based doublets in metastatic non-small-cell lung cancer. An Italian Trials in Medical Oncology study

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Background: Many patients with advanced non-small-cell lung cancer (NSCLC) do not tolerate cisplatin-based regimens because of its nonhemathological toxicity.

Patients and methods: We evaluated the response rate safety of new platinum analogue regimens, randomizing 147 patients with nonoperable IIIB/IV NSCLC to (i) carboplatin (area under the curve = 5 mg min/ml) on day 1 plus gemcitabine (GEM) (1000 mg/m^2) on days 1 and 8 for six cycles; (ii) same regimen for three cycles followed by docetaxel (Taxotere) (40 mg/m^2) on days 1 and 8 plus GEM (1250 mg/m^2) on days 1 and 8 for three cycles; (iii) oxaliplatin (130 mg/m^2) on day 1 plus GEM (1250 mg/m^2) on days 1 and 8 for six cycles.

Results: Intention-to-treat objective response rates were 25%, 25% and 30.6% in arms A, B and C, respectively. Median survival was 11.9, 9.2 and 11.3 months in arms A, B and C, respectively. Grade 3/4 neutropenia/anemia occurred in 29%/12.5%, 10%/16.5% and 8%/6% of arms A, B and C, respectively; grade 3/4 thrombocytopenia in 20.5%, 16.5% and 6%; grade 1/2 neurological toxicity in 43% of arm C.

Conclusions: Oxaliplatin/GEM (arm C) had similar activity to carboplatin/GEM (arm A), but milder hematological toxicity and may be worth testing in a phase III study against carboplatin/GEM in patients not suitable for cisplatin. The sequential regimen gave no additional benefit.

Key words: first-line chemotherapy, NSCLC, phase II study, platinum analogs

introduction

Platinum-based chemotherapy is considered the standard treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC). The combination cisplatin plus gemcitabine (GEM) is one of the most active, with an overall response rate of 30%–38%, and median survival of 8–10 months in phase III trials [1, 2]. Although other doublets have produced similar results in several randomized trials [3, 4], a recent meta-analysis indicated that, in combination with a platinum agent, GEM confers a survival advantage over other drugs, with an absolute 1-year survival benefit of 3.9% compared with other platinum-therefore necessary to develop new treatment strategies characterized by milder toxicity profile.

Carboplatin and oxaliplatin, platinum compounds with a mechanism of action similar to that of cisplatin [6], have lower nephro, hematological and gastrointestinal toxicity than cisplatin, are easier to use in the outpatient setting, and do not require specific hydration. Because of these advantages and apparently comparable efficacy, carboplatin and oxaliplatin present as attractive alternatives to cisplatin in combination with GEM in advanced NSCLC.

Carboplatin plus GEM appears to be superior to, or as effective as, other regimens including mitomycin, ifosfamide

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Since most patients die of progressive disease (PD), even if they initially respond well to chemotherapy, a sequential combination approach, according to the mathematical model of Norton Day and [14] offers the opportunity to use drugs of different mechanisms of action, to reduce the risk of cross-resistance. In this context, docetaxel appears useful, in view of its proven efficacy in NSCLC after platinum failure [15].

We designed an open-label, randomized, multicentric, three-arm phase II study to evaluate the efficacy and tolerability of different platinum combinations in stage IIIB/IV NSCLC. Two of the three arms were determined on the basis of the work of Iaffaioli et al. [16] and preliminary results of two studies from our group [17, 18]. In the first [17], preclinical and clinical findings indicated that administration of carboplatin [area under the curve (AUC) = 5 mg min/ml, day 1] before GEM (1000 mg/m^2, days 1–8) gave the better outcome. In the second study [18], performed on a population of highly pretreated patients to determine the appropriate dose of oxaliplatin in association with constant GEM dose, it was found that oxaliplatin can be administered safely at 130 mg/m^2 every 3 weeks combined with GEM 1250 mg/m^2 on days 1 and 8 of a 21-day cycle. In the third arm, carboplatin/GEM, at the same dose and schedule reported above for three cycles was followed by docetaxel/GEM for three cycles. Docetaxel/GEM is one of best nonplatinum regimens, and appears as a rational alternative to the cisplatin-based doublet in this setting [19].

patients and methods

patient eligibility

Patients with cytohistologically confirmed stage IIIB/IV NSCLC were eligible for this study, provided they had not received prior chemotherapy. Patients with recurrence after surgery were eligible. Additional eligibility criteria were performance status (PS) of 2 or less according to the Eastern Cooperative Oncology Group scale, age ≤75 years (patients >70 years were eligible if PS ≤1), no brain metastasis, and life expectancy ≥12 weeks. Other requirements included adequate bone marrow (leukocyte count above 4.0×10^9 per l, platelet count above 120×10^9 per l) hepatic and renal function, and negative baseline pregnancy test in women. Patients with a significant history of cardiac disease or evidence of current central or peripheral neuropathy were ineligible. Those with previous cancer were also ineligible (except adequately treated carcinoma of skin or cervix) unless they had been in complete remission for at least 5 years. In addition, patients had to be willing and able to attend for scheduled visits, and comply with the treatment plan, laboratory tests and other trial procedures.

All eligible patients were assessed before registration by physical examination; chest X-ray; computed tomography of the chest, upper abdomen and brain; abdominal ultrasonography; bone scan or skeletal X-ray; fiberoptic bronchoscopy if indicated and complete blood determination. Signed and dated informed consent was obtained from all registered patients indicating that the patient (or a legally acceptable representative) had been informed of all pertinent aspects of the trial. The study was approved by the National Cancer Institute of Milan Ethics Committee and by the ethics committee of each participating center. The study was conducted in accordance with ethical principles embodied in the Declaration of Helsinki and good clinic practice guidelines.

treatment plan

Eligible patients were registered centrally and randomized to receive one of the three schedules (Figure 1). Patients in arm A received carboplatin (AUC = 5 mg min/ml) on day 1 plus GEM (1000 mg/m^2) on days 1 and 8 for six cycles. Patients in arm B received the same regimen for three cycles followed by docetaxel (40 mg/m^2) on days 1 and 8 plus GEM (1250 mg/m^2) on days 1 and 8 for three cycles. Patients in arm C received oxaliplatin (130 mg/m^2) on day 1 plus GEM (1250 mg/m^2) on days 1 and 8 for six cycles. Blood counts were performed on days 1 and 8 before infusion, then weekly. Hepatic and renal functions were evaluated at each cycle on day 1. Cycles were repeated every 3 weeks if absolute granulocyte count (AGC) was $\geq 1.5 \times 10^9$ per l and platelet count was $\geq 100 \times 10^9$ per l. If grade ≥2 hematological toxicity occurred on day 1, treatment could be delayed for 1 week. If toxicity persisted, the treatment was administered as follows: if AGC was between 1.0 and 1.5×10^9 per l and platelet count between 75 and 100×10^9 per l, doses were reduced by 25%; if AGC was $\leq 1.0 \times 10^9$ per l and platelet counts $\leq 75 \times 10^9$ per l, treatment was delayed by a further week; subsequently if AGC remained low, the cycle was considered concluded. If grade ≥2 hematological toxicity was documented on day 8, treatment was delayed for 1 week. In the event of persistent toxicity, the treatment cycle was considered concluded and the patient was restarted on the next cycle at the third week. Patients were not allowed any other anticancer drugs. Growth factor support, antiemetics and therapy for sensory neuropathies were permitted at the investigator's discretion. In responding patients and patients with stable disease (SD), a maximum of six cycles of chemotherapy was given. Patients were removed from the study for PD, unacceptable toxicity (as defined by the protocol or determined by the treating physician) or patient refusal.

RANDOMIZATION

...e rate and ...aseline; ...ve response ...te response (CR) was defined as disappearance of all disease. For patients with measurable disease, a partial response (PR) was defined as ≥50% decrease of the sum of the products of the largest perpendicular diameters of all measurable lesions. For CR and PR, confirmation by assessment not less than 4 weeks after the initial observation was necessary. SD was defined as <50% decrease or <25% increase in the sum of the products of the diameters of the lesions with no new lesions appearing. PD was defined as a >25% size increase of at least one measurable lesion, or appearance of a new lesion. Patients could be assessed at any time in the event of suspected disease progression.

Secondary end points were time to progression (TtP) and overall survival (OS). TtP was the time from randomization to disease progression, death or last known follow-up. OS was time from randomization to death or last known follow-up. Intention-to-treat analyses of response rate, TtP and OS were performed. Duration of response was defined as time from initial documentation of response to failure (disease progression or death).

Safety was evaluated in all patients who received at least one cycle. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria version 2.0 [21].

statistical analysis

The trial was conducted using the Bryant and Day [22] two-stage design. For the sample size calculation, type I and II errors were assumed as 0.10; a response rate of 40% and severe acute toxicity rate (grades 3 and 4) of ≤10% were considered sufficient to warrant further investigation, whereas a response rate of 20% and severe acute toxicity rate of 30% were considered unacceptable. Stage I of the study required 17 patients to be enrolled in each arm; if ≤4 responses or ≥5 severe acute toxic effects were observed on either arm, the trial was to be prematurely closed. Otherwise, the trial would proceed to stage II and accrual continues until 46 eligible patients were enrolled in each arm. If ≥13 responses and ≤10 severe acute toxic effects occurred in any arm, the regimen of that arm was considered worthy of further testing.

Statistical analysis included simple descriptive statistics (medians for continuous variables and proportions for categorical data). Confidence intervals (CIs) of proportions were calculated from the exact binomial distribution. Progression-free survival and OS curves were estimated with the Kaplan-Meier method.

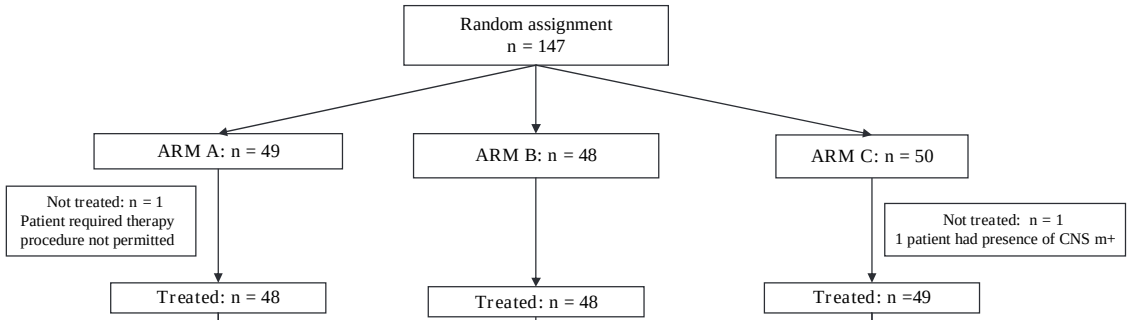
results

patient characteristics

From October 2001 to November 2004, 147 patients (49 in arm A, 48 in arm B and 50 in arm C) were enrolled in the study from six Italian centers (Figure 2). On review, two patients were ineligible and were excluded from the analysis: one (arm A) did not receive the study drugs because of deterioration in PS and the other (arm C) had brain metastases. The three arms were reasonably well balanced as indicated by patient characteristics (Table 1). A total of 132 (90.3%) of 145 assessable patients had stage IV disease. The most prominent histology was adenocarcinoma (64%) with male predominance (72%). Median age was 62 years, range 27–75. Seventeen patients were >70 years of age.

efficacy

Intent-to-treat responses in each study arm, together with objective response rates (ORRs), are given in Table 2. Per protocol ORRs were 26.7% (95% CI 14.6–41.9) in arm A, 27.9% (95% CI 15–43.7) in arm B and 33.3% (95% CI 20–49) in arm C. Median response duration was 8.2 months (range 5.9–9.6) in arm A, 6.3 months (range 5.0–15.0) in arm B, 5.4 months (range 3.4–9.3) in arm C. With a median follow-up of 27 months,



	patients		patients		patients	%
Randomized	49		48		50	
Received treatment	48	99	48	100	49	99
Age, years						
Median (range)	61.5 (41–74)		60 (27–72)		64 (36–75)	
Sex						
Male	32	67	37	77	36	73
Female	16	33	11	23	13	27
ECOG performance status						
0	30	63	24	50	30	61
1	17	35	23	48	18	37
2	1	2	0	0	1	2
Missing	0	0	1	2	0	0
Histological classification						
Adenocarcinoma	33	69	31	65	29	59
Epidermoid	7	15	7	15	9	18
Bronchioloalveolar	–		2	4	1	2
Other NSCLC	8	16	8	16	10	21
TNM staging						
IIIB	3	6	3	6	7	14
IV	45	94	45	94	42	86
Disease extent						
M+ sites = 1	29	60	21	44	22	45
M+ sites > 1	19	40	27	56	27	55
Previous surgery for neoplastic disease						
Yes	7	15	14	29	12	24
No	41	85	34	71	37	76
If yes, type of surgery						
Palliative	2		1		3	
Curative	2		5		5	
Diagnostic	3		8		4	
Abnormal lactate dehydrogenase	7	15	13	27	6	12

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; TNM, tumor–node–metastasis.

Table 2. Intent-to-treat responses in the three treatment arms

	Arm A (n = 48)		Arm B (n = 48)		Arm C (n = 49)	
	No. of patients	%	No. of patients	%	No. of patients	%

median TtPs were 6.4 (range 4.9–8.2), 4.9 (range 4.0–7.2) and 5.8 (range 4.5–7.8) months in arms A, B and C, respectively (Figure 3). Median survival times were 11.9 (range 9.7–15.8), 9.2 (range 7.5–12.2) and 11.3 months (range 8.3–13.4) in arms A, B and C, respectively (Figure 4).

Estimated 1- and 2-year survival rates were 48.5% (95% CI 36.0–65.4) and 24.9% (95% CI 14.4–43.2) in arm A; 36.3% (95% CI 24.7–53.3) and 13.4% (95% CI 5.7–31.8) in arm B and 48.1% (95% CI 35.4–65.3) and 14.1 (95% CI 6.1–32.5) in arm C.

treatment administration and safety

A total of 652 cycles were administered: 230 in arm A, 199 in arm B and 223 in arm C. Details of treatment administration including dose intensity and dose delay are shown in Table 3. Hematological toxicity is shown in Table 4. Grade 3–4 neutropenia occurred in 29% of patients in arm A, 10% in arm B and 8% in arm C. Grade 3–4 anemia occurred in 12.5%, 6% and 2% of patients in arms A, B and C, respectively. Grade 3–4 thrombocytopenia occurred in 20.5%, 16.5% and 6% of patients in arms A, B and C, respectively. Symptomatic bleeding was not observed in any arm. Nonhematological

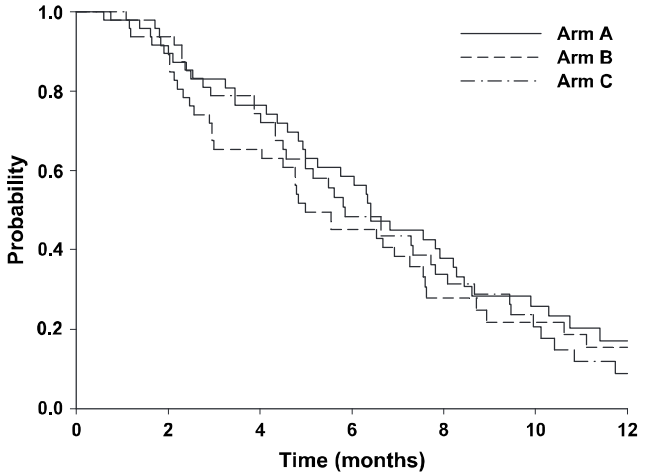
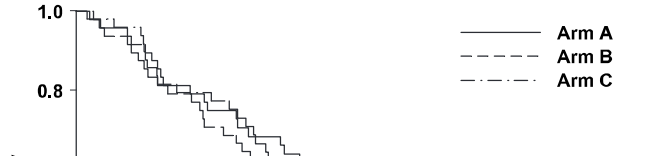


Figure 3. Progression-free survival.



...never ...fairly ...g and ...elated to the use of oxaliplatin, occurred in 45% of patients and consisted of grade 1–2 reversible paresthesia in all cases. In patients >70 years, no grade 3/4 toxicity was observed.

discussion

This three-arm randomized phase II study was carried out to indicate hypotheses regarding efficacy and tolerability in the widely used doublet carboplatin/GEM, in oxaliplatin/GEM and in a sequential carboplatin/GEM followed by the nonplatinum regimen docetaxel/GEM.

The carboplatin/GEM combination is increasingly used in Europe and the United States as a consistently effective first-line chemotherapy in advanced NSCLC [23]. Two meta-analyses [9, 24] found that cisplatin-based was superior to carboplatin-based chemotherapy in terms of responses but this did not translate into better survival. By contrast, a meta-analysis to assess the feasibility of substituting carboplatin for cisplatin in combination with GEM or docetaxel showed no marked differences in efficacy between cisplatin- and carboplatin-containing regimens, although a slight trend favoring carboplatin/GEM was observed. Furthermore, a comparison of toxicity profiles indicated that carboplatin/GEM was less toxic [25].

In the present trial, we had an ORR of 25% (2 CR and 10/48 PR) with carboplatin/GEM. This is within the range 19.6%–33.3% obtained in other trials using similar schedules (not all randomized) [10, 26–29], but lower than reported by other experiences [7, 28] in which the ORR was >40%. The present ORR was also lower than that obtained in our previous single-institution study of four carboplatin/GEM schedules (35%), and much lower than the 50% ORR obtained in the same study when carboplatin was given before GEM. However, the latter finding was probably a random overestimate, arising from the selection process in which this regimen was chosen as the best of the four tested.

In spite of this disappointing ORR, median survival time and 1-year and 2-year survival in the carboplatin/GEM arm of present study were somewhat better than in our previous experience [17]: 11.9 months, 48.5% and 24.9% versus 11 months, 44% and 11%. Furthermore, median and 1-year survival in this study were similar to those reported using more intensive carboplatin/GEM regimens, in which GEM was given at a higher dose (1250 mg/m^2) [26, 27].

Similar median and 1- to 2-year survival results were obtained recently in a phase III randomized study conducted by the London Lung Cancer Group. In this study, carboplatin/GEM was significantly more effective than MIC with low-dose cisplatin (50 mg/m^2) [7]. Moreover, the smaller randomized phase III study of the Czech Lung Cancer Cooperative Group, which compared a 3-week carboplatin/GEM schedule with cisplatin (80 mg/m^2)/GEM did not translate the longer duration of response of the cisplatin/GEM arm into a significant survival advantage [10].

Although well tolerated, easy to administer in the outpatient setting, and associated with less nonhematological toxicity than cisplatin, carboplatin/GEM is often associated with secondary hematological effects, principally thrombocytopenia [7, 10, 27]. Our experience was that carboplatin/GEM was associated with grade 3/4 neutropenia, anemia and thrombocytopenia in 29%, 12.5% and 20.5% of patients, respectively. These results appear worse than those obtained in the sequential and oxaliplatin/GEM arms.

With regard to our sequential arm results, we note that the docetaxel/GEM combination has recently been shown to produce similar OS to the well-known cisplatin/vinorelbine regimen but with less toxicity [19]. However, in our study, which employed this promising regimen in sequence after carboplatin/GEM, there was no additional benefit relative to the doublet alone (ORR 25% in both arms, median survival 11.9 and 11.3 months). Furthermore, the toxicity profile of the sequential arm was intermediate between that of carboplatin/GEM and oxaliplatin/GEM. Moreover, while not experiencing clinically significant toxicity, arm B (sequential arm) patients were characterized by lower compliance resulting in premature

Table 3. Treatments administered

	Arm A	Arm B	Arm C
Total number of cycles	230	199	223
Median number of cycles (min–max)	6 (1–6)	4 (1–6)	6 (1–6)
No. of delayed cycles (%)	44 (19.1)	30 (15.1)	23 (10.3)
Median dose intensity	0.79	0.87	0.88

ed at least one cycle of treatment

	Arm A (n = 48)			Arm B (n = 48)			Arm C (n = 49)		
	1–2	3	4	1–2	3	4	1–2	3	4
Allergic reaction	2			4			8		
Anorexia	2			2			4		
Asthenia	25	10		25	6		16	4	
Diarrhea	8	2		10			16		
Edema						2		2	
Flu-like syndrome	2			10	2		4	4	
Infection	4			8	2		6		
Liver toxicity	6	2		4			2	2	2
Mucositis	4			4	2		2	2	
Nausea/vomiting	56	6		52	6		65	2	2
Neuromotor (TIA)								2	
Pain	2			6			2	4	
Paresthesia	2			4			43		
Pulmonary dyspnea						2	2		
Rash	8			10			4		
Renal toxicity	6	2		2					
Central venous thrombosis				2	2				

TIA, transient ischemic attack.

discontinuation in some cases (total cycles given 199, versus 230 in arm A and 223 in arm C). Our results with the sequential regimen are consistent with recent experience with carboplatin/GEM followed sequentially by docetaxel alone [29] in which the sequential regimen results were similar to those obtained with other standard doublets and did not represent a significant improvement in the treatment of advanced NSCLC.

We found that arm C (oxaliplatin/GEM) had an ORR of 30.6% (1 CR and 14/49 PR) which is slightly better than the 25% ORR of the other two arms. It is noteworthy, in addition, that we were able to deliver the planned therapy to most patients in arm C: median dose intensity 0.88 versus 0.79 in arm A (carboplatin/GEM); delayed cycles 10.3% versus 19.1% in arm A (Table 3). This result is also slightly better than the ORR of 25% and median survival of 7.3 months reported by another Italian trial—the only one with a comparable chemo-naive patient population (85% stage IV) [30]. Our better results may be due to the fact that the other Italian study used a lower GEM dose (2000 mg/m^2 versus 2500 mg/m^2) and included 6.7% of patients with brain metastases, while we excluded patients with unfavorable prognostic factors. The toxicity profile of both of oxaliplatin/GEM, in the context of similar survival and efficacy to carboplatin/GEM, indicates that the former may be worth testing in a noninferiority phase III study against carboplatin/GEM particularly in patients with advanced NSCLC not suitable for cisplatin. Finally, in view of their ease of administration, oxaliplatin and carboplatin doublets may, in this patient setting, lend themselves to integration with new targeted therapies (e.g. antibodies to growth factors and growth factor receptors) which promise to be the future in advanced NSCLC.

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