Cancer Chemother Pharmacol (2008) 61:803–807
DOI 10.1007/s00280-007-0537-1

ORIGINAL ARTICLE

Gemcitabine, ifosfamide and paclitaxel in advanced/metastatic non-small cell lung cancer patients: a phase II study

F. V. Piantedosi · F. Caputo · G. Mazzarella · M. Gilli · A. Pontillo · D. D'Agostino · S. Campbell · S. A. Marsico · A. Bianco

Received: 8 May 2007 / Accepted: 25 May 2007 / Published online: 18 July 2007

Abstract Although platinum-based two-drug combinations represent the elective therapeutic approach for advanced/metastatic NSCLC, there is still interest in exploring the efficacy and tolerability of platinum-free combinations including third generation agents in selected NSCLC population. Based on the satisfying activity of gemcitabine (G), ifosfamide (I) and paclitaxel (T) as single agents in NSCLC, we have designed a phase II study to explore an alternative approach to platinum-containing regimens using a combination of these three drugs. To investigate the activity/toxicity of T 175 mg/m^2 on day 1, I 3 g/m^2 on day 1 (with Mesna uroprotection) and G 1,000 mg/m^2 on day 1–8, every 3 weeks in the treatment of advanced/metastatic NSCLC, 46 patients (38 male, 8 female) with NSCLC were enrolled: mean age 58 (range 33–70); Stage IIIB/IV = 15/31; ECOG PS 0-1/2 = 31/15; Histology: adenocarcinoma = 20, squamous = 14, large cell = 3, NSCLC = 8, adenosquamous = 1. A total of 221 cycles have been administered (median number 4.8 for patients). In intent-to-treat analysis, partial response was achieved in 17 patients (36.95%), stable disease and progressive disease was detected in 16 (34.78%) and 10 (21.73%) patients, respectively. Time to progression was 30.9 weeks; median survival time was 42.7 weeks; the survival rates at 12 and 18 months were 34.79 and 15.21%, respectively. No toxic deaths occurred. No patients experienced grade 4 neutropenia and thrombocytopenia. Neutropenia grade 3 occurred in 10 patients (21.7%); Anemia grade 3 in 1 (2.1%); Thrombocytopenia grade 2 in two patients (4.3%) and grade 3 in one (2.1%). Peripheral neuropathy grade 1 occurred in ten (21.7%) and grade 2 in two patients (4.3%). Additional non-haematological toxicities were mild nausea, emesis and fatigue. GIT is well tolerated and active regimen in both advanced and metastatic NSCLC. These data suggest future investigations for GIT schedule as a possible alternative to platinum-based regimens in selected advanced/metastatic NSCLC patients where survival, tolerability and quality of life are the primary goals.

Keywords Gemcitabine · Ifosfamide · Paclitaxel · Platinum-free · Chemotherapy · NSCLC

F. V. Piantedosi · F. Caputo · G. Mazzarella · M. Gilli · A. Pontillo · D. D'Agostino · S. A. Marsico
Department of Medical-Surgical Oncology and Thoracic Diseases, AORN Monaldi, Via L Bianchi, 80131 Naples, Italy

S. Campbell · A. Bianco (✉)
Department of Health Sciences, Faculty of Medicine and Surgery, University of Molise, Via F De Sanctis, 86100 Campobasso, Italy
e-mail: andrea.bianco@unimol.it

Introduction

The current practice for treating advanced/metastatic non-small cell lung cancer (NSCLC) includes the administration of platinum-based chemotherapy regimens. Although no combination has emerged as gold standard, addition of newer generation agents such as vinorelbine, gemcitabine, paclitaxel, docetaxel or irinotecan to a platinum agent represents the most common approach to advanced NSCLC [1–4].

Despite the clear survival benefit of platinum-containing regimens, demonstrated in 1995 by the meta-analysis from the NSCLC collaborative group [5], both physicians and patients continued to be concerned about the potential debilitating side effects coupled with small survival gains. In addition, platinum-based regimens in patients with poor

performance status, in which the presence of co-morbidities amplifies the severity of toxicities, should not represent the compulsory therapeutic option.

Third generation agents are well tolerated and have shown single agent activity that is equal to or greater than cisplatin [6]. This has prompted interest to evaluate the efficacy of new platinum-free combinations [7–9].

Evidence indicates that front-line non-platinum-based regimens, with their favourable toxicity profile, exhibit similar activity in terms of response rate and overall survival as platinum-based combinations [10–14].

Efficacy together with acceptable toxicity in NSCLC patients has also been reported with non-platinum-based triplet therapy [15].

Current international guidelines, however, recommend the use of platinum-based chemotherapy for patients with good performance status [16]. The reasons for preferring a platinum-based regimen are determined by higher response rate and survival, although toxicity remains a major concern.

A literature-based meta-analysis has demonstrated that the survival advantage of platinum- versus non-platinum-based chemotherapy is not statistically significant [17]. Indeed, in the subset of trials with third generation agents, the authors did not find significant differences in survival comparing platinum and non-platinum regimens, but significant benefits, in terms of toxicities such as anemia, neutropenia, thrombocytopenia, nausea, vomiting and toxic death rate, for platinum-free regimens. The same subset of trials confirmed a better response rate for platinum-containing regimens suggesting that platinum-containing regimens should be used in patients with advanced NSCLC in which the tumor size reduction represents a primary goal. This has reopened the debate on the potential benefits of non-platinum regimens over platinum-based chemotherapy in advanced NSCLC.

Based on the satisfying activity of gemcitabine (G) [18, 19], ifosfamide (I) [20] and paclitaxel (T) [21] as single agents in NSCLC, we have designed a phase II study to explore the overall survival (OS) and tolerability of a non-platinum triplet combination (GIT).Response rate and time to progressive disease (TtPD) were the secondary end-points.

The schedule of the GIT-triplet utilized in this phase II study has been gemcitabine (1,000 mg/m^2 day 1, 8), ifosfamide (3,000 mg/m^2 plus mesna day 1) and paclitaxel (175 mg/m^2 day 1), every 3 weeks.

Patients and methods

Eligibility

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) cytological or histological confirmation of non-small cell lung cancer (NSCLC); (2) unresectable or metastatic disease (stage IIIB, both pleural effusion or supra-clavicular lymph-nodes) or IV, suitable for neither surgery nor radiotherapy; (3) bi-dimensional measurable lesions; (4) age $\leq$70 years; (5) performance status (PS) $\leq$2 on eastern cooperative oncology group (ECOG) scale; (6) absence of clinical or radiological evidence of brain metastases; (7) chemotherapy naive; (8) no previous or concomitant malignancy (except for cutaneous basocellular carcinoma and uterine cervical carcinoma in situ); (9) adequate bone marrow function (neutrophil count >2,000 mm^{-3}, PLT >100,000 mm^{-3}, Hb >10 g/dl); (10) adequate liver function (AST, ALT and bilirubin <1.25 of UNV) and adequate renal function (serum creatinine <1.5 mg/dl).

Other inclusion criteria were life-expectancy >4 months, no significant or active cardiovascular disease, no significant endocrine or metabolic disease.

Written informed consent was obtained from each patient before entering the study.

The study was approved by the local ethics committee and was conducted in accordance with ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice.

Baseline and follow-up assessment

Pre-treatment evaluation included patient's medical history, physical examination, chest X-ray, fiber-bronchoscopy, brain–chest CT-scan, abdomen–pelvis ultrasonography and bone scan.

Complete blood cell count (CBC), biochemistry assessment for liver and kidney function and ECG wer performed before every cycle (day 1).

Re-staging was scheduled after three and six courses of treatment following the same medical procedure performed for pre-study evaluation. Response assessment was performed according to WHO criteria for evaluation. Toxicity was evaluated every week following WHO recommendations.

Treatment plan and dose adjustment

Gemcitabine 1,000 mg/m^2 was administered as a 30-min i.v. infusion on days 1 and 8 of each course. Ifosfamide (I) 3,000 mg/m^2 of body surface area with mesna for uroprotection on day 1 and paclitaxel (T) 175 mg/m^2 as a 3-h i.v. infusion on day 1 (*GIT-"triplet"*). Mesna was administered intravenously as 20% of the total ifosfamide dose just before the ifosfamide infusion and as 40% of the total dose after 4 and 8 h. Cycles were repeated every 3 weeks.

Dose adjustment was performed according to hematological and non-hematological toxicities. For grade 3–4 hematological toxicities, chemotherapy doses were delayed (for up 2 weeks) and were reduced by 25%. Doses were reduced by 25% for any non-haematological toxicities (excluding nausea, vomiting and alopecia). Patients not recovering, respectively, within 2 weeks for haematological and 3 weeks for non-haematological toxicities were withdrawn from the trial.

Statistics

Sample size is computed according to the Simon two-step method design. Assuming to obtain a response rate of at least 25% in the treatment group, and 5% in a hypothetical control group, considering an error alpha = 5%, and an error beta = 90%, study population is calculated as follows: first step, the study shall be stopped if no response is recorded in the first nine patients; second step, the activity of this treatment is rejected if less than three responses are recorded in the first 32 patients. If the rate of estimated protocol violation is 20%, the overall target size population is 38 patients.

Results

Patient characteristics

Forty-six patients (38 males, 8 females) affected by NSCLC were enrolled in this phase II trial at the Unit of Pneumo-Oncology of "Monaldi" High Specialization Hospital, Naples, Italy. Patients characteristics are listed in Table 1.

The patients were treated with GIT-"triplet" [G (1,000 mg/m^2 days 1, 8) plus I (3,000 mg/m^2 day 1 plus mesna) plus T (175 mg/m^2 day 1), every 3 weeks]. The median age of the patients was 58 years (range 33–70 years) and the ECOG performance status was 0–1 in 31 patients and 2 in 15 patients. Fifteen patients were affected by stage IIIB and 31 by stage IV NSCLC. Histopathology was adenocarcinoma (20 patients), squamous (14 patients), and others non-small cell (12 patients).

Chemotherapy administration

Overall 221 courses were delivered; the median number of cycles administered for patient was 4.8. Forty-three out of 46 enrolled patients were assessable for response and toxicity (35 males and 8 females). Two out of the three ruled out patients did not start treatment, the other was lost to follow-up.

Response rate and survival

The overall follow-up time for all patients was 30 months.

Table 1 Patient demographics and disease characteristics

Variable	No. patients
Gender	
Male	38 (82.6%)
Female	8 (17.4%)
Stage	
IIIB	15 (32.6%)
IV	31 (67.4%)
Median age	58
Range	33–70
ECOG P.S.	
0–1	31 (67.4%)
2	15 (32.6%)
Histology	
Adenocarcinoma	20 (43.5%)
Squamous	14 (30.4%)
Others	12 (26.1%)
Evaluable patients	43/46 (93.5%)
Males	35/43 (81.4%)
Females	8/43 (18.6%)
Not assessable for response	3/46 (6.5%)

In intent-to-treat analysis, 17 patients showed a partial response (36.95%); there were 16 patients with stable disease (34.78%) and 10 patients (21.73%) with progressive disease; three patients were not assessable for response (6.52%) (Table 2). There were no significant differences in the response rate according to PS, stage and histology.

The median overall survival in intent-to-treat analysis was 42.7 weeks (95% C.I. 39.2–51.7) and the survival rates at 12 and 18 months were 34.79 and 15.21%, respectively. Median time to progression (TTP) was 30.9 weeks (95% C.I. 26.9–36) (Table 2).

Toxicity

No toxic deaths were recorded. None of the patient experienced febrile neutropenia and/or thrombocitopenia WHO

Table 2 Response and survival: intent to treat analysis

Outcome	Results
Partial response	17/46 (36.95 %)
Stable disease	16/46 (34.78 %)
Progressive disease	10/46 (21.73 %)
Not assessable for response	3/46 (6.52 %)
Median TTP (weeks)	30.9 (95% C.I. 26.9–36)
Median survival (weeks)	42.7 (95%.C.I. 39.2-51.7)
12-months survival (%)	34.79
18-months survival (%)	15.21

Table 3 WHO hematologic and nonhematologic patient toxicity (%)

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	15.2	10.8	2.1	0
Neutropenia	19.5	15.2	21.7	0
Febbrile neuropenia	0	0	0	0
Thrombocytopenia	8.6	4.3	2.1	0
Nausea/vomiting	26	17.3	8.6	0
Peripheral neuropathy	21.7	4.3	0	0
Hemorrhagic cystitis	0	0	0	0
Fever	10.8	6.5	0	0
Asthenia	13	8.6	0	0

grade 4. WHO grade 3 neutropenia were observed in 21.7% of the patients; grade 3 anemia in 2.1% of patients; grade 2 thrombocytopenia in 4.3% of patients and grade 3 in 2.1%. Peripheral neuropathy grade 1 in 21.7% and grade 2 in 4.3% of patients. Nausea and vomiting grade 1 in 26%, grade 2 in 17.3%, grade 3 in 8.6%. Grade 1 asthenia in 13%, grade 2 in 8.6%. Grade 1 fever in 10.8%, grade 2 in 6.5%. None of the patients experienced hemorrhagic cystitis (Table 3).

Discussion

In this phase II trial, the combination of gemcitabine plus ifosfamide plus paclitaxel (GIT-"Triplet") has shown a good activity in terms of both survival and response rate in advanced and metastatic NSCLC.

A satisfying 36.95% overall response rate has been achieved and the median overall survival is 42.7 weeks.

Potential benefits of new generation non-platinum regimens over platinum-based chemotherapy in advanced NSCLC have been reported in a literature based meta-analysis [17] showing no differences in survival comparing platinum and non-platinum regimens, with significant benefits in terms of toxicity for platinum-free regimens including third generation agents.

The GIT schedule that we have proposed is an active and well tolerated new triplet combination without cisplatin.

Toxicities experienced in our trial were acceptable and easy to manage, contributing to better quality of life.

The new platinum-free triplet regimen has potential advantages in patient where toxicities are a major concern for therapeutic management.

Till date, cisplatin-free regimens are preferred in elderly patients because of the age-related reduction of the functional reserve of important organs [22, 23] as well as in those patients where the presence of co-morbidities make palliation and symptom containment, the main goal of chemotherapy.

Our data are attractive if we consider that the majority of the enrolled patients exhibited metastatic disease and poor performance status suitable for palliative treatments.

Good overall survival with acceptable toxicity and quality of life achieved in stage IV patients makes the GIT schedule proposed a promising chemotherapy option for metastatic NSCLC patients where the response in term of tumor size reduction is not a primary therapeutic target.

Following on from our phase II study results, a large phase III randomized trial is required where the activity of GIT is compared to standard cisplatin-based regimens in stage IIIB/IV NSCLC patients.

References

1. Belani CP, Fossella F (2005) Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). Cancer 104(12):2766–2774
2. Bonomi P, Kim K, Fairclough D, Cella D, Kugler J, Rowinsky E, Jiroutek M, Johnson D (2000) Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern cooperative oncology group trial. J Clin Oncol 18:623–631
3. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. J Clin Oncol 12:360–367
4. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, Mattson K, Manegold C, Palmer MC, Gregor A, Nguyen B, Niyikiza C, Einhorn LH (2000) Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 18:122–130
5. Non-small cell lung cancer collaborative group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899–909
6. Bunn PA Jr, Kelly K (1998) New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clin Cancer Res 4:1087–1100
7. Pujol JL, Quantin X, Choma D, Jacot W, Khial F (2002) Combination chemotherapy without cisplatin in the treatment of advanced non-small cell lung cancer. Lung Cancer 38(Suppl 3):S57–S60 Review
8. Recchia F, Saggio G, Cesta A, Candeloro G, Rea S (2005) Paclitaxel plus gemcitabine in advanced non-small cell lung cancer patients with low performance status. Anticancer Res 25(1B):409–414
9. Ichinose Y, Seto T, Semba H, Itoh K, Inoue Y, Tanaka F, Araki J, Tamanoi M, Yamamoto H, Iwamoto N (2005) UFT plus gemcitabine combination chemotherapy in patients with advanced non-small-cell lung cancer: a multi-institutional phase II trial. Br J Cancer 93(7):770–773
10. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis I (2001) Platinum-based

and nonplatinum-based chemotherapy in advanced non-small cell lung cancer: a randomized multicentre trial. Lancet 357:1478–1484
11. Georgoulias V, Ardavanis A, Tsiafaki X, Agelidou A, Mixalopoulou P, Anagnostopoulou O, Ziotopoulos P, Toubis M, Syrigos K, Samaras N, Polyzos A, Christou A, Kakolyris S, Kouroussis C, Androulakis N, Samonis G, Chatzidaki D (2005) Vinorelbine plus cisplatin vs docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 23:2937–2945
12. Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, Manzione L, Barbera S, Frontini L, Veltri E, Findlay B, Cigolari S, Myers R, Ianniello GP, Gebbia V, Gasparini G, Fava S, Hirsh V, Bezjak A, Seymour L, Perrone F (2003) Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21(16):3009–3010
13. Kosmidis P, Mylonakis N, Nicolaides C, Kalophonos C, Samantas E, Boukovinas J, Fountzilas G, Skarlos D, Economopoulos T, Tsavdaridis D, Papakostas P, Bacoyiannis C, Dimopoulos M for the Hellenic Cooperative Oncology Group (2002) Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 20:3578–3585
14. Smit E, van Meerbeeck J, Lianes P, Debruyne C, Legrand C, Schramel F, Smit H, Gaafar R, Biesma B, Manegold C, Neymark N, Giaccone G (2003) Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group-EORTC 08975. J Clin Oncol 21:3909–3917
15. Baldini E, Ardizzoni A, Prochilo T, Cafferata MA, Boni L, Tibaldi C, Neumaier C, Conte PF, Rosso R (2001) Italian lung cancer task force. Gemcitabine, ifosfamide and navelbine (GIN): activity and safety of a non-platinum-based triplet in advanced non-small-cell lung cancer (NSCLC). Br J Cancer 85(10):1452–1455
16. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR (2004) American Society of Clinical Oncology: treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22:330–353
17. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA (2005) Platinum-based versus non–platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 23:2926–2936
18. Le Chevalier T (1996) Single-agent activity of gemcitabine in advanced non-small cell lung cancer. Semin Oncol 23(5 Suppl 10):36–42
19. Kelly K (1999) The role of single-agent gemcitabine in the treatment of non-small-cell lung cancer. Ann Oncol 10(Suppl 5):S53–S56
20. Eberhardt W, Niederle N (1992) Ifosfamide in non-small cell lung cancer: a review. Semin Oncol 19(Suppl 1):40–48
21. Hainsworth JD, Thompson DS, Greco FA (1995) Paclitaxel by 1-hour infusion: an active drug in metastatic non-small-cell lung cancer. J Clin Oncol 13(7):1609–1614
22. Balducci L, Hardy CL, Lyman GH (2000) Hemopoietic reserve in the older cancer patient: clinical and economic considerations. Cancer Control 7(6):539–547
23. Balducci L (2000) Geriatric oncology: challenges for the new century. Eur J Cancer 36(14):1741–1754