Vinorelbine and oxaliplatin in stage IV nonsmall cell lung cancer patients unfit for cisplatin: a single-center experience

Olivier Mir, Jérôme Alexandre, Stanislas Ropert, Vincent Montheil, Idalie Martin, Jean-Philippe Durand and François Goldwasser

Many patients with stage IV nonsmall cell lung cancer (NSCLC) are unfit for cisplatin-based chemotherapy because of poor performance status, impaired renal function or severe comorbidity. We documented the feasibility of a combination of weekly vinorelbine and biweekly oxaliplatin in a population of stage IV NSCLC patients unable to receive cisplatin. Fifty-five chemo-naive patients (40 males, median age 60 years, range 43–84) were treated on an outpatient basis, and received every 2 weeks: vinorelbine 25 mg/m^2 intravenously on day 1 and 60 mg/m^2 orally on day 8, and oxaliplatin 85 mg/m^2 intravenously on day 1. Patients were considered unfit for cisplatin because of performance status ≥ 2 (30 patients), impaired renal function (17 patients) or severe comorbidities (eight patients). Twenty-two patients (40%) had two or more metastatic sites, and 14 (25%) had central nervous system metastases. A total of 288 cycles were given (median per patient: 4, range 1–11). The planned dose intensity of vinorelbine was administered in 65% of patients. One complete and 13 partial responses were observed, providing an objective response rate of 26% (95% confidence interval: 14.4–37.6). The median progression-free survival and overall survival were 3.5 months and 9.5 months, respectively. The 1-year survival rate was 24% (95% confidence interval: 12.7–35.3). The main grade 3/4 toxicities were: neutropenia (15 patients, 27%), anaemia (12 patients, 22%) and peripheral neuropathy (eight patients, 15%). Three patients (5.5%) experienced febrile neutropenia. In a nonselected NSCLC patient population, the vinorelbine–oxaliplatin doublet had clinical activity in the same range as cisplatin-based combinations. This doublet allows combining a platinum derivative with a sustained dose intensity of vinorelbine in unfit patients. *Anti-Cancer Drugs* 20:105–108 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2009, **20**:105–108

Keywords: chemotherapy, elderly, nonsmall cell lung cancer, oxaliplatin, vinorelbine

Department of Medical Oncology, Université Paris Descartes, Assistance Publique – Hôpitaux de Paris, Teaching Hospital Cochin, Paris, France

Correspondence to Dr Olivier Mir, MD, MSc, MPH, Department of Medical Oncology, Teaching Hospital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, Faculté de Médecine, 27, rue du faubourg Saint-Jacques F75014 Paris, France
Tel: +33 630 739 079; fax: +33 158 411 745;
e-mail: olivier.mir@cch.aphp.fr

Received 9 July 2008 **Revised form accepted** 8 October 2008

Introduction

Platinum-based chemotherapy is the standard of care for the initial treatment of patients affected by advanced nonsmall cell lung cancer (NSCLC) with good performance status (PS), adequate renal function and limited comorbidities [1].

However, a large proportion of patients with advanced NSCLC are considered ineligible for cisplatin-based chemotherapy because of poor PS, renal dysfunction and/or cardiovascular and respiratory comorbidities (considered as a risk for forced hydration) [2,3]. Therefore, it is admitted that patients with a PS ≥ 2 do not benefit from cisplatin-based chemotherapy [2]. Indeed, the Eastern Cooperative Oncology Group 1594 study showed that advanced NSCLC patients with a PS of 2 did not tolerate chemotherapy regimens containing first or second-generation platinum derivatives (cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/docetaxel, carboplatin/paclitaxel) [4,5]. Carboplatin was proposed as an alternative to cisplatin in patients with impaired renal function [6]. In elderly patients, however, the exact evaluation of creatinine clearance is difficult and therefore precludes exact carboplatin dose adjustment [7,8]. In addition, a recent meta-analysis strongly suggested that carboplatin provided response rate in NSCLC inferior to that observed with cisplatin [9]. These data confirm that treatments designed specifically for the subset of patients not eligible for cisplatin or carboplatin-based combinations are needed.

Oxaliplatin is a third-generation platinum derivative (diaminocyclohexane platinum) that displays activity against a broad spectrum of tumours, including NSCLC [10]. Noteworthy, oxaliplatin is not nephrotoxic, has low haematological toxicity, and its toxicity is not dependent on creatinine clearance. Thus, oxaliplatin can be administered safely without specific hydration in an outpatient setting [11]. We report here a single-centre experience with a combination of vinorelbine and oxaliplatin in stage IV NSCLC patients unable to receive cisplatin.

0959-4973 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32831cdb51

Patients and methods

Chemo-naïve patients with a diagnosis of stage IV NSCLC were discussed by the multidisciplinary staff of thoracic oncology of our institution. They were considered ineligible for cisplatin when they had one or more of the following criteria: WHO PS ≥ 2, estimated creatinine clearance less than 60 ml/min, severe cardiac comorbidity precluding the forced hydration required for cisplatin administration. Between October 2003 and 2007, oxaliplatin–vinorelbine combination was proposed to all patients ineligible for cisplatin and patients for whom the life expectancy was more than 3 months. All patients were asked to provide informed consent. We report here data obtained from all patients receiving at least one cycle.

Vinorelbine (25 mg/m^2) was given as a 15-min infusion on day 1, with oxaliplatin (85 mg/m^2) as a 2-h infusion the same day. On day 8, vinorelbine was given orally at a dose of 60 mg/m^2, without checking of blood cell count. No specific hydration was given, both drugs being devoid of nephrotoxicity. All patients received antiemetic prophylaxis on day 1, consisting of standard doses of 5-hydroxytryptamine-3-receptor antagonists and corticosteroids. Cycles were repeated every 14 days until progression or intolerable toxicity.

Chemotherapy was administered if, on day 1 of treatment, the absolute neutrophil count was greater than 500/mm^3 and the platelet count was greater than 80 000/mm^3; if counts were not adequate, then therapy was delayed until recovery. The doses of both drugs were administered at 75% of the planned dose if any of the following toxicities occurred: neutropenic fever with hospitalization and/or intravenous antibiotics, grade 3 (associated with bleeding) or 4 thrombocytopenia and any grade ≥ 3 nonhaematological toxicity (except nausea/emesis).

Patients were evaluable for tumour response when they had at least one bi-dimensionally measurable lesion outside a previously irradiated area. Tumour evaluation was performed every 4 cycles of treatment, or before if clinically indicated, according to WHO criteria [12]. Toxicity was assessed according to the National Cancer Institute-Common Toxicity Criteria v2.0 and oxaliplatin-specific scale [13]. Clinical benefit was defined as a 50% decrease in analgesic drugs requirements or improvement of PS. Progression-free survival and overall survival were measured from the date of first treatment administration to the date of disease progression or death for the former and the date of death for the latter.

Results

During the period from October 2003 to 2007, 142 patients diagnosed with stage IV NSCLC requiring chemotherapy were treated in our department. Amongst them, 55 patients were found ineligible for cisplatin-based chemotherapy, and received the above-described combination of vinorelbine and oxaliplatin in the outpatient setting.

The patients' characteristics are shown in Table 1. The median age was 60 years (range 43–84 years). The main reason for cisplatin ineligibility was PS ≥ 2 in 30 patients, creatinine clearance less than 60 ml/min in 17 patients and severe comorbidities in eight patients. Twenty-two patients (40%) had two or more metastatic sites, and 14 patients (25%) had brain metastases. As altered nutritional and inflammatory status correlates with increased risk of severe haematological toxicity [14], it is of interest to point out that 38 patients (69%) had elevated baseline C-reactive protein levels (>5 mg/l) and 13 patients (24%) had baseline prealbumin levels less than 0.25 mg/l.

Toxicity

The median number of cycles given per patient was 4 (range 1–11), for a total of 288 cycles. The planned vinorelbine dose intensity was given in 65% of patients. The main grade 3/4 toxicities were: neutropenia [15 patients, 27%, 95% confidence interval (CI): 15.5–39.0] and anaemia (12 patients, 22%, 95% CI: 10.9–32.7). Three patients (5.5%, 95% CI: 0–11.5) experienced febrile neutropenia. No toxic death occurred. Nausea and emesis were mild (grade 1–2 only) and occurred in 54% of patients. Grade 1–2 constipation occurred in 44% of patients. Forty-nine patients (89%, 95% CI: 80.9–97.3) presented grade 1/2 neurotoxicity, the most common manifestations being transient acral cold-related dysesthesia (69% of patients) and acute pharyngeolaryngeal dysesthesia (11% of patients). Grade 3 peripheral neuropathy occurred in eight patients (15%, 95% CI: 5.2–23.9). In all patients, the underlying renal or cardiac function impairment remained stable and no acute aggravation requiring medical intervention was noticed.

Table 1 Patients baseline characteristics ($n=55$)

Characteristics	*n* (%)
Sex: M/F	40/15 (73/27)
WHO PS: 0/1/2/3	0/25/23/7 (0/45/42/12)
Primary tumour histology	
Adenocarcinoma	28 (51)
Giant cell carcinoma	14 (26)
Squamous cell carcinoma	6 (11)
Other	7 (12)
Number of metastatic sites	
1	32 (58)
2	16 (30)
≥ 3	7 (12)
Patients with CNS metastases	14 (25)

CNS, central nervous system; F, female; M, male; PS, performance status.

Table 2 Response rate in all patients ($n=55$)

Response	*n* (%, 95% confidence interval)
Complete response	1 (2, 0–5.4)
Partial response	13 (23, 12.4–34.9)
Stable disease	17 (31, 18.7–43.1)
Progressive disease	22 (40, 27.1–53.0)
Failure (early death or not evaluable)	2 (4)

Table 3 Characteristics of responding patients

Characteristics	Responding patients	Nonresponding patients
n	14	41
Median age (range), years	62 (43–83)	59 (43–83)
Sex: M/F (%)	11/3 (79/21)	29/12 (71/29)
WHO PS: 1/2/3 (%)	8/5/1 (57/36/7)	17/18/6 (41/44/15)
Number of metastatic sites: *n* (%)		
1	9 (65)	23 (56)
2	4 (28)	12 (29)
≥ 3	1 (7)	6 (15)
Patients with CNS metastases (%)	4 (29)	10 (24)

CNS, central nervous system; F, female; M, male; PS, performance status.

Activity

All but two patients were evaluable for tumour response (Table 2). One complete and 13 partial responses were observed, providing an objective response rate of 26% (95% CI: 14.4–37.6). The median progression-free survival and overall survival were 3.5 months and 9.5 months, respectively. The 1-year survival rate was 24% (95% CI: 12.7–35.3). Amongst 19 patients with pain, 10 (53%) had clinical benefit. Six patients had an improvement of PS. The characteristics of responding patients are presented in Table 3. No statistical difference was observed in nonresponding patients, except a better baseline PS (median: 1 vs. 2, $P = 0.03$).

Amongst the seven patients with a baseline PS of 3, we observed one partial response, two stable diseases and four progressive diseases. Grade 3 neutropenia occurred in two patients, and no other grade 3–4 toxicity was observed. Median progression-free survival and overall survival were 3 months (range 0–9) and 7 months (5–19), respectively.

Discussion

This single-institution experience with the vinorelbine–oxaliplatin doublet in stage IV NSCLC patients ineligible for cisplatin-based regimens suggests that combination chemotherapy may represent effective palliation, with a favourable toxicity profile in this subset of patients.

Cisplatin-based chemotherapy is a cornerstone in the management of advanced NSCLC, with response rates of 20–30% [1]. However, cisplatin-induced toxicities (emesis, renal failure and haematological toxicity) worsen the quality of life, especially in elderly patients and/or in patients with significant comorbidities or altered PS. Noteworthy, oxaliplatin has a broad spectrum of clinical activity, which not only reflects the antitumoral activity of cisplatin [15], but is even wider with well-demonstrated clinical activity in colorectal cancer patients [16]. Furthermore, oxaliplatin showed low cross-resistance to cisplatin in in-vitro studies, being therefore an attractive option in patients resistant or refractory to cisplatin [17,18].

Single-agent oxaliplatin provided a 15% objective response rate in poor prognosis NSCLC patients, suggesting that oxaliplatin has similar activity and a better toxicity profile than cisplatin [17]. Oxaliplatin-based combinations are attractive in unfit NSCLC patients as they may improve the therapeutic index [18,19].

The combination of vinorelbine and oxaliplatin was the first oxaliplatin-based doublet evaluated in advanced NSCLC patients [20,21]. Monnet *et al.* studied this combination in 28 selected patients (93% had a PS of 0 or 1, and all had a creatinine clearance > 60 ml/min and no severe comorbidity). Patients received a fixed dose of oxaliplatin (130 mg/m^2) on day 1, combined with vinorelbine (25 mg/m^2) on days 1 and 8, every 3 weeks. The objective response rate was 35% (95% CI: 17–56%) and the 1-year survival rate was 37%, with manageable toxicity in the outpatient setting. Given that the vinorelbine–cisplatin combination showed its superiority over platinum alone and vinorelbine alone [22,23], but also equal efficacy on paclitaxel–carboplatin regimen [24,25], one may expect that the vinorelbine–oxaliplatin regimen may provide an improved therapeutic index [21].

Compared with the previously published phase II study of vinorelbine and oxaliplatin in NSCLC patients [21], we observed a lower response rate in our patient population (26 vs. 35%), which was probably because of the poorer baseline clinical characteristics of our patients. Indeed, in our study, the median age was slightly older (60 vs. 58 years), the PS was poorer (PS 2 and 3: 55 vs. 7%), and more patients had brain metastases (25 vs. 11%).

However, in our series, the toxicity profile and tolerance of the vinorelbine–oxaliplatin combination were good in this frail population. In particular, the proportion of patients who experienced grade 3–4 neutropenia was lower than in the study of Monnet *et al.* (27 vs. 57%), despite the poorer baseline characteristics of our patient population and the increased dose intensity of vinorelbine. This lower incidence of grade 3–4 neutropenia is probably because of the fact that vinorelbine was given orally on day 8 without checking the blood cell count. In contrast, the incidence of grade 3 oxaliplatin-induced peripheral neuropathy was higher in our study (15 vs. 7%), despite similar dose intensity for oxaliplatin (median 42.5 mg/m^2/week vs. 43.3 mg/m^2/week). The explanation of this higher neurological toxicity could be the increased

number of administrations, and thus an increased cumulative dose of oxaliplatin.

Finally, other oxaliplatin-based doublets have been evaluated in advanced NSCLC patients. In a randomized phase II study, Le Chevalier *et al.* [26] found similar activities for the doublets gemcitabine–cisplatin and gemcitabine–oxaliplatin, with less toxicity with the oxaliplatin-based regimen. Hence, the doublet gemcitabine–oxaliplatin seems a valuable option in frail NSCLC patients [19]. The use of gemcitabine, however, precludes concomitant radiotherapy, and other active agents such as vinorelbine therefore deserve further evaluation in this setting.

Taken together, these studies and our experience suggest that oxaliplatin-based doublets display clinical activity in the same range to that observed with cisplatin-based regimens, together with a favourable toxicity profile making them attractive in frail patients.

Conclusion

In this study, the vinorelbine–oxaliplatin combination was active in NSCLC patients, with a favourable toxicity profile. Although further comparative studies are required to determine the respective roles of oxaliplatin, carboplatin and cisplatin in NSCLC, this combination may represent a therapeutic opportunity for patients ineligible for cisplatin-based and/or carboplatin-based regimens.

References

1 Loriot Y, Soria JC, Le Chevalier T. Expanding role of chemotherapy in lung cancer. *Ann Oncol* 2006; **17** (**Suppl 10**):x101–x107.

2 Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, *et al*. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. *Ann Oncol* 2004; **15**:419–426.

3 Gridelli C, Langer C, Maione P, Rossi A, Schild SE. Lung cancer in the elderly. *J Clin Oncol* 2007; **25**:1898–1907.

4 Gridelli C. Chemotherapy of non-small cell lung cancer in the elderly. *Lung Cancer* 2002; **38** (**Suppl 3**):S67–S70.

5 Gridelli C. Does chemotherapy have a role as palliative therapy for unfit or elderly patients with non-small-cell lung cancer? *Lung Cancer* 2002; **38** (**Suppl 2**):S45–S50.

6 Von Hoff DD. Whither carboplatin?–A replacement for or an alternative to cisplatin? *J Clin Oncol* 1987; **5**:169–171.

7 Takimoto CH, Remick SC, Sharma S, Mani S, Ramanathan RK, Doroshow J, *et al*. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. *J Clin Oncol* 2003; **21**:2664–2672.

8 Marx GM, Blake GM, Galani E, Steer CB, Harper SE, Adamson KL, *et al*. Evaluation of the Cockroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. *Ann Oncol* 2004; **15**:291–295.

9 Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, *et al*. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007; **99**:847–857.

10 Goldwasser F, Misset JL. Clinical use of oxaliplatin in solid tumors. *Bull Cancer* 2001; **88**:S40–S44.

11 Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**:1053–1071.

12 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**:207–214.

13 Caussanel JP, Levi F, Brienza S, Misset JL, Itzhaki M, Adam R, *et al*. Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rythmmodulated rate compared with constant rate. *J Natl Cancer Inst* 1990; **82**:1046–1050.

14 Alexandre J, Gross-Goupil M, Nguyen M-L, Gornet J-M, Misset J-L, Goldwasser F. Evaluation of the nutritional and inflammatory status of cancer patients to assess the risk of severe hematologic toxicity of antineoplastic regimens. *Ann Oncol* 2003; **14**:36–41.

15 Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, *et al*. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Institute's anticancer drug screen panel. *Biochem Pharmacol* 1996; **52**:1855–1865.

16 Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**:229–237.

17 Monnet I, Brienza S, Hugret F, Voisin S, Gastiaburu J, Saltiel JC, *et al*. Phase II study of oxaliplatin in poor-prognosis non-small cell lung cancer (NSCLC). ATTIT. Association pour le traitement des tumeurs intra thoraciques. *Eur J Cancer* 1998; **34**:1124–1127.

18 Cortinovis D, Bidoli P, Zilembo N, Fusi A, Bajetta E. Oxaliplatin doublets in non-small cell lung cancer: a literature review. *Lung Cancer* 2008; **60**:325–331.

19 Franciosi V, Barbieri R, Aitini E, Vasini G, Cacciani GC, Capra R, *et al*. Gemcitabine and oxaliplatin: a safe and active regimen in poor prognosis advanced non-small cell lung cancer patients. *Lung Cancer* 2003; **41**:101–106.

20 Monnet I, Soulié P, de Cremoux H, Saltiel-Voisin S, Bekradda M, Saltiel JC, *et al*. Phase I/II study of escalating doses of vinorelbine in combination with oxaliplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2001; **19**:458–463.

21 Monnet I, de Cremoux H, Soulié P, Saltiel-Voisin S, Bekradda M, Saltiel JC, *et al*. Oxaliplatin plus vinorelbine in advanced non-small-cell lung cancer: final results of a multicenter phase II study. *Ann Oncol* 2002; **13**:103–107.

22 Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, *et al*. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1998; **16**:2459–2465.

23 Depierre A, Chastang C, Quoix E, Lebeau B, Blanchon F, Paillot N, *et al*. Vinorelbine versus vinorelbine plus cisplatin in advanced non-small cell lung cancer: a randomized trial. *Ann Oncol* 1994; **5**:37–42.

24 Ramsey SD, Moinpour CM, Lovato LC, Crowley JJ, Grevstad P, Presant CA, *et al*. Economic analysis of vinorelbine plus cisplatin versus paclitaxel plus carboplatin for advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2002; **94**:291–297.

25 Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, *et al*. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001; **19**:3210–3218.

26 Le Chevalier T, Thezenas S, Breton J, Pujol J, Coudert B, Sun X, *et al*. *J Clin Oncol* 2006; **24** (**Suppl 18**). ASCO Annual Meeting Proceedings Part I: 7097 (abstract).