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Gemcitabine and vinorelbine as second-line therapy in non-small-cell lung cancer after prior treatment with taxane + platinum-based regimens

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Abstract

Treatment options in patients with recurrent non-small-cell lung cancer (NSCLC) remain limited as a result of the poor activity of older agents after platinum-based therapy. The present phase II study aimed to evaluate the combination of gemcitabine and vinorelbine in patients with relapsed NSCLC after pretreatment with taxane + platinum-based regimens, since gemcitabine has demonstrated activity in that setting and the combination has been well tolerated in previous phase I/II studies. Patients with advanced NSCLC (stages III/IV), World Health Organization (WHO), Performance Status (PS) $\leqslant 2$, prior platinum + taxane-based chemotherapy and unimpaired haematopoietic and organ function were eligible. Chemotherapy was administered as follows: vinorelbine 25 mg/m^2 followed by gemcitabine 1000 mg/m^2, both administered on days 1 and 8, recycled every 3 weeks. 40 patients were entered and 39 were evaluable for response and all 40 for toxicity: median age was 61 years (range 50–72 years), median PS = 1 (range 0–2), gender ratio = 37 males/3 females, stages at initial diagnoses were IIIA = 2, IIIB = 14, IV = 24. Metastatic sites included: lymph nodes: 23, bone: 4, liver: 5, brain: 4, lung nodules: 9, adrenals: 8, pleural effusion: 4. 22 patients had prior paclitaxel/ifosfamide/cisplatin treatment. Objective responses were; partial response (PR): 9/40 (22.5%), stable disease (SD): 13/40 (32.5%) and progressive disease (PD) 18/40 (45%). The median time-to-progression (TTP) was 4.5 months (range 1–17 months) and median survival 7 months (range 2–17 + months). 1-year survival was 17%. Grade 3 neutropenia was seen in 33% of patients. There was no grade 4 neutropenia and no episodes of febrile neutropenia. No grade 3/4 thrombocytopenia or grade 3/4 other non-haematological toxicities were observed. The combination of gemcitabine/vinorelbine is active and well tolerated in patients with advanced NSCLC failing prior taxane/platinum therapy. This regimen represents a tolerable and effective combination to apply in the palliative treatment of relapsed NSCLC.

Keywords: Non-small-cell lung cancer; Chemotherapy; Gemcitabine; Vinorelbine; Docetaxel; Paclitaxel; Ifosfamide; Cisplatin

1. Introduction

Despite significant improvements in the management of advanced (stages IIIB/IV) non-small-cell lung cancer (NSCLC) the vast majority of stage IIIB and all stage IV patients will develop progressive disease. Treatment options regarding second-line chemotherapy have been limited so far and it was hard until recently to retrieve any data providing convincing evidence that demonstrates the benefit of chemotherapeutic agents in treating relapsed/refractory disease over best supportive care (BSC). However, the first such randomised study of docetaxel versus BSC has now been reported [1]. Recently, the introduction of several newer cytotoxic agents, such as taxanes, gemcitabine, vinorelbine and irinotecan, with demonstrated activity in NSCLC has resulted in an improved outcome with first-line treat-

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ments incorporating these agents with platinum drugs. Most new drug/platinum-based combinations have demonstrated higher activity and improved survival figures when compared with single-agent cisplatin [2–4].

For a long time, second-line chemotherapy in NSCLC has not been given much consideration due to the notoriously poor outcome when applying traditional cytotoxic agents. However, more recently, taxanes, and in particular docetaxel, have demonstrated reproducible activity and therapeutic value in relapsed, platinum-pretreated NSCLC patients [1,5,6]. Gemcitabine, an analogue of deoxycytidine, a pyrimidine antimetabolite, has recently demonstrated satisfactory activity when administered as second-line treatment in NSCLC [7–9].

Vinorelbine, a vinca alkaloid analogue, with definite activity in NSCLC represents an agent that, due to its favourable toxicity profile, can be combined with other active agents in this setting. However, its value has recently been questioned in NSCLC patients exposed to prior platinum-based treatments [10]. Currently, as many more patients with advanced NSCLC derive clinical benefit with tolerable newer first-line regimens, more patients with good performance status (PS) and function would be candidates for some form of second-line treatment. Given that most patients with advanced NSCLC are treated in the first-line with standard or experimental taxane + platinum-based regimens, it appears particularly attractive to combine gemcitabine and vinorelbine in relapsed or refractory disease.

In the present phase II study, we evaluated the activity, survival and toxicities of the gemcitabine/vinorelbine regimen in patients with advanced NSCLC that had progressed during or after standard doublet paclitaxel/carboplatin or experimental triplet paclitaxel/ifosfamide/cisplatin (PIC) [11] and docetaxel/ifosfamide/cisplatin (DIP) (data not shown) first-line regimens.

2. Patients and methods

2.1. Patient selection

Patients with histologically confirmed advanced NSCLC, stage IIIA/IIIB and IV at diagnosis, that had relapsed after or progressed on a taxane + platinum analogue combination regimen and had never received gemcitabine and vinca alkaloid drugs were candidates for the present study. Eligibility included: (i) histologically confirmed NSCLC that had progressed on or relapsed after first-line taxane + platinum-based chemotherapy; (ii) World Health Organization (WHO) PS $\leqslant 2$; (iii) life expectancy $\geqslant 3$ months; (iv) adequate haematopoietic (absolute neutrophil count (ANC) $\geqslant 1.5\times10^9$/l, platelet count (PLT) $\geqslant 100\times10^9$/l), liver (bilirubin <25.65 μmol/l, aspartate aminotransferase (AST)/alamine aminotransferase (ALT) $<2\times$upper normal limit (nl), unless caused by tumour and serum albumin >3.0 g/l) and renal function blood urea nitrogen (BUN) and creatinine <1.5 nl; nl = 1.5 mg/dl = 132.6 μmol/l in our laboratory or creatinine clearance >0.83 ml/s; (v) progression during or after the completion of prior chemotherapy with a taxane + platinum analogue regimen; paclitaxel/ifosfamide/cisplatin (PIC) [11,12], docetaxel/ifosfamide/cisplatin (data not shown), and paclitaxel/carboplatin; (vi) absence of active coronary artery disease (in the form of unstable angina or myocardial infarction over the last 12 months), unstable diabetes mellitus, or peripheral neuropathy $\geqslant$grade 2 by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC); (vii) no prior irradiation to areas encompassing $>30\%$ of marrow-bearing bone. Patients with brain metastases were eligible provided that they had received brain irradiation and had no evidence of progressive or symptomatic disease at this site; and (viii) presence of bi-dimensionally measurable or evaluable disease outside a previously irradiated field, unless definite evidence of progression at this site. The study was approved according to Institutional policies and informed consent obtained from each patient before study entry.

2.2. Treatment schedule

Eligible patients were treated as follows: vinorelbine was administered at 25 mg/m^2 diluted in 100 ml 0.9% normal saline (N/S) over 15 min by intravenous (i.v.) infusion, followed by gemcitabine at 1000 mg/m^2 diluted in 250 ml 0.9% N/S over 30 min by i.v. infusion. Antiemetic medications included 8 mg of ondasetron or 3 mg of granisetron i.v. over 15 min just before the chemotherapy drugs. No subsequent antiemetic drug doses were planned unless the patient experienced nausea or vomiting, in which case he was instructed to take additional per os doses of ondasetron 8 mg t.i.d. or granisetron 1 mg every day (q.d.) until nausea/vomiting resolved, usually for 1–2 days postchemotherapy. In the case of $\geqslant$grade 2 nausea/vomiting dexamethasone 8 mg was added with the standard 5-HT3 antagonist before chemotherapy drug administration. Both vinorelbine and gemcitabine were administered as described on days 1 and 8 of each cycle and recycled every 21 days.

2.3. Supportive care

In cases of grade 4 neutropenia, granulocyte-colony stimulating factor (G-CSF) 5 μg/kg subcutaneously (s.c.)/day was to be administered until the white blood cell (WBC) count was $\geqslant 5\times10^9$/l at least 48 h before the next chemotherapy cycle. For an inadequate ANC on day 1 of treatment, and after an appropriate delay for the return of ANC to $\geqslant 1.5\times10^9$/l, G-CSF was to be administered in the subsequent cycles until 48 h before chemotherapy. Recombinant human erythropoietin

(rh-Epo) was to be given 10.000 IU s.c. t.i.w. (not on chemotherapy days) whenever a drop of haemoglobin (Hb) $\leqslant 105$ g/l was observed and continued until the Hb level reached $\geqslant 120$ g/l.

2.4. Dose modifications

The prerequisites for dose modifications were set as follows: (i) any episode of grade 4 neutropenia of >5 days duration, (ii) any episode of febrile neutropenia $\geqslant$ grade 3, (iii) any episode of grade 4 thrombocytopenia requiring platelet transfusions, (iv) any non-haematological grade 3 or 4 toxicity excluding nausea and vomiting, flu-like illness and alopecia.

The following guidelines were to be applied with respect to dose reductions for toxicity: (i) for neutropenia, meeting the aforementioned criteria, both gemcitabine and vinorelbine doses were reduced by 20% in subsequent cycles and if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles treatment was stopped; however, the patient was evaluable for toxicity and response. (ii) For grade 4 thrombocytopenia requiring platelet transfusions, reduction of gemcitabine and vinorelbine by 20% was applied as specified for neutropenia. (iii) For $\geqslant$ grade 3 mucositis, the doses of gemcitabine and vinorelbine were reduced by 20% in subsequent cycles. (iv) For neuropathy $\geqslant$ grade 3 treatment was interrupted.

In cases where the blood counts had not recovered to ANC $\geqslant 1.5\times10^9$/l and PLT $\geqslant 100\times10^9$/l on day 1 of therapy, treatment was withheld until recovery, and after a maximum delay of 2 weeks no further therapy was administered in cases where the counts did not return to normal, otherwise G-CSF was administered prophylactically in subsequent cycles as specified earlier. In the case of ANCs $= 1$–1.5×10^9/l and/or PLT $= 75$–100×10^9/l on day 8, both drugs were given after a 20% dose reduction. Whenever the ANC was $\leqslant 1\times10^9$/l and/or the PLT was $\leqslant 75\times10^9$/l on day 8, no treatment was given on that day and subsequent doses were reduced by 20% for both drugs throughout treatment.

2.5. Pretreatment, follow-up studies and response evaluation

Tumour measurements were performed by physical examination and the specific radiological test that documented measurable disease before treatment. Computed tomography (CT) scans of the chest, abdomen and brain (if indicated or in cases of irradiated brain metastases) and bone scans were carried out within 2 weeks before study entry. For positive bone scans, X-rays or CTs of the involved bony structure were performed. Clinical examination, full blood counts, biochemical tests, appropriate serum tumour marker measurements and a chest X-ray were carried out before each cycle of therapy. Blood counts were checked on the days of treatment (days 1 and 8) and weekly thereafter, or every 3 days in cases of neutropenia until full recovery. Evaluation of response was performed every two cycles of therapy. Patients experiencing toxic death despite objective responses at measurable sites would be categorised as treatment failures. Complete remission (CR) was defined as the disappearance of all signs and symptoms of disease for at least 1 month, with the documented disappearance of all known lesions by physical examination, X-rays, CT scans, bone scans, and the development of no new lesions. Partial remission (PR) was indicated by a decrease of 50% or greater (compared with pretreatment measurements) in the sum of the products of the two largest perpendicular diameters of all measurable lesions and no concomitant growth of new lesions for at least 1 month. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Stable disease (SD) was defined as less than 50% decrease or up to 25% increased over pretreatment measurements with no concomitant growth of new lesions for at least 1 month. Progressive disease (PD) was defined as an increase of 25% or greater over the original measurements in the sum of the products of the two largest perpendicular diameters of any measurable lesions or the appearance of new lesions, and relapse was defined as occurring following a period of response when a former lesion reappeared or enlarged as above or a new lesion appeared. Full staging evaluation had to be performed, as reported above, before treatment initiation. Follow-up disease evaluation was performed at approximately 3-monthly intervals after the end of treatment.

2.6. Statistical methods

Patients who received at least two cycles of treatment were evaluable for response and patients who received at least one cycle of treatment were evaluable for toxicity. Response duration was measured from the day of its initial documentation until confirmed disease progression; time to progression was calculated from study entry until evidence of progressive disease; overall survival was measured from the day of entry until last follow-up or death. Actuarial survival was estimated by the product-limit method of Kaplan and Meier [13].

Confidence intervals for response rates (RRs) were calculated according to the method described by Simon [14]. The sequential two-step statistical test of Gehan [15] was applied in order to define the number of patients required to detect activity of treatment. It was calculated that with an anticipated RR of approximately 20% (minimum level of activity) the sample size required for having confidence limits of $\pm 7\%$ would be 40 patients.

3. Results

3.1. Patient characteristics

40 patients entered the present study and their characteristics are shown in Table 1; 39 received at least two cycles of therapy and were evaluable for response and all were evaluable for toxicity. One patient developed PD soon after the first cycle and was considered as a non-responder. 16 patients (40%) were refractory to first-line treatment, while the remaining 24 (60%) were taxane + platinum-sensitive and relapsed after a prior response (Table 1).

3.2. Response to treatment and survival

Objective responses were; PR: 9/40 (22.5%; 95% confidence interval (CI) = 10.8–38.5%), SD: 13/40 (32.5%; 95% CI = 18.6–49.1%) and PD: 18/40 (45%; 95% CI = 29.3–61.5%). The RR to gemcitabine/vinorelbine in patients refractory to first-line treatment was 3/16 (19%; 95% CI = 4.1–45.6%), while the RR in patients with sensitive disease was 6/24 (25%; 95% CI = 9.8–46.7%), which did not differ significantly. The median time-to-progression (TTP) was 4.5 months (1–17+) and median survival 7 months (2–17+). 1-year survival was 17% (Fig. 1).

3.3. Toxicities

Toxicities are shown in Table 2. Grade 3 neutropenia was seen in 33% of patients without any grade 4 neutropenia and no episodes of febrile neutropenia were observed. However, 11 patients (28%) required G-CSF administration for treatment delays on day 1 as a result of an inadequate ANC. None of the patients included in the present study required red blood cell transfusions since rh-Epo was initiated whenever a drop of Hb $\leqslant$ 105 g/l was seen and continued until Hb $\geqslant$ 120 g/l. 14 patients (35%) required rh-Epo and oral iron supplementation at some time during treatment, usually after the third or fourth chemotherapy cycle. No grade 3/4 thrombocytopenia or other grade 3/4 non-haematological toxicities were encountered. Mild asthenia/fatigue was seen in 13% of patients, usually after the fourth chemotherapy cycle. 3 patients (2 grade 2 and 1 grade 1) developed a syndrome of dyspnoea, cough, fever and diffuse pulmonary infiltrates on chest X-rays, that responded to oral corticosteroids and did not lead to treatment discontinuation in any of the cases. This was considered as gemcitabine-related alveolitis (pneumonitis), while the contribution of vinorelbine (vinca alkaloid) cannot reliably be excluded.

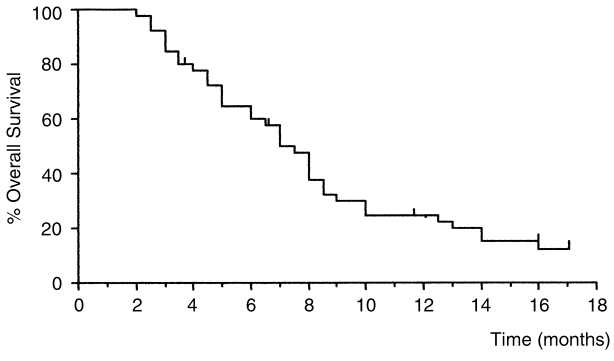

Fig. 1. Actuarial survival analysis of patients with non-small-cell lung cancer (NSCLC) treated with the gemcitabine/vinorelbine second-line combination chemotherapy regimen after relapse or non-response to taxane + platinum-based regimens (Kaplan–Meier plot).

3.4. Compliance to treatment

A total of 170 treatment courses were administered; the median number of courses per patient was 4 (range

Table 1
Patient Characteristics

Characteristic	no. (%)
Total patients	40 (100)
Sex	
Male	37 (93)
Female	3 (8)
Age (years)	
Median 61 (range 50–72)	
Performance status (WHO)	
0	10 (25)
1	23 (58)
2	7 (18)
Stage at initial diagnosis	
IIIA	2 (5)
IIIB	14 (35)
IV	24 (60)
Histology	
Squamous	15 (38)
Adenocarcinoma	20 (50)
Large cell	5 (13)
Prior non-medical therapy	
Surgery	11 (28)
Radiotherapy	20 (50)
Previous first-line chemotherapy	
Paclitaxel/ifosfamide/cisplatin	22 (55)
Docetaxel/ifosfamide/cisplatin	12 (30)
Paclitaxel/carboplatin	6 (15)
Metastatic sites at relapse	
Liver	5 (13)
Bone	4 (10)
Brain	4 (10)
Lung nodules	9 (23)
Adrenals	8 (20)
Pleural effusion	4 (10)
Lymph nodes	23 (58)
No. of metastatic sites	
1	8 (20)
2 or more	32 (80)

Table 2
Toxicities (NCI-common toxicity criteria (CTC) grade) of gemcitabine/vinorelbine ($n=40$)

Toxicity	NCI-CTC grade (% of patients, all cycles)				
	0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
(i) Haematological					
Leucopenia	5 (12)	9 (23)	12 (30)	14 (35)	0
Neutropenia	6 (14)	6 (15)	15 (38)	13 (33)	0
Thrombocytopenia	35 (87)	3 (8)	2 (5)	0	0
Anaemia	18 (44)	17 (43)	5 (13)	0	0
(ii) Non-haematological					
Nausea and vomiting	30 (74)	9 (23)	1 (3)	0	0
Mucositis	39 (97)	1 (3)	0	0	0
Peripheral neuropathy	19 (47)	18 (45)	3 (8)	0	0
Diarrhoea	36 (90)	4 (10)	0	0	–
Alopecia	18 (45)	18 (45)	4 (10)	0	0
Cutaneous (rash)	31 (77)	7 (18)	2 (5)	0	0
Hepatic	37 (92)	3 (8)	0	0	–
Asthenia/fatigue	35 (87)	5 (13)	0	0	–
Flu-like syndrome	38 (95)	2 (5)	0	–	–
Pulmonary	37 (92)	1 (3)	2 (5)	0	0

1–6). Dose reductions or omissions for myelosuppression on day 8 were required in 8 (20%) of patients. The median delivered dose-intensity was 83% (range: 60–100%) of the planned dose-intensity. 24 (60%) patients received $\geqslant 75\%$ of the planned dose-intensity for both gemcitabine and vinorelbine.

4. Discussion

As an increasing proportion of patients with advanced NSCLC derive clinical benefit and prolonged survival with novel drug/platinum combinations, such as paclitaxel/carboplatin, docetaxel/cisplatin, vinorelbine/cisplatin and gemcitabine/cisplatin, it is anticipated that many of these patients will require some type of salvage chemotherapy after relapse. Based on past experiences, such an option was rather limited given that response rates were low with platinum-based first-line regimens, PS was poor as a result of uncontrollable disease or prolonged disability from prior chemotherapy (e.g. peripheral neuropathy as a result of cisplatin/vinca alkaloid drug therapy), and no single agents at that time had demonstrated appreciable activity after failure of cisplatin-based regimens, as suggested by a large randomised study reported by the Eastern Cooperative Oncology Group in 1989 [16]. The RR of 22.5%, that we observed in the present study with gemcitabine/vinorelbine as a second-line treatment in advanced NSCLC, appears adequately encouraging for further evaluation.

One recent report evaluating the weekly gemcitabine 1000 mg/m^2-vinorelbine 20 mg/m^2 regimen, with both drugs given on days 1, 8, 15/every 4 weeks in 55 patients with relapsed or resistant NSCLC, demonstrated an objective RR of 18% with a median TTP of 5 months, median survival of 6.5 months and a 1-year survival of 20% [17]. It is important to note that 47/55 (85%) of the patients had prior first-line treatment both with a taxane and a platinum agent. Moreover, despite the apparently 11% higher planned dose-intensity for gemcitabine in their study compared with our regimen, 40% of the planned doses on day 15 were omitted due to myelosuppression [17]. Similar to the study of Hainsworth and colleagues [17], all our patients were pretreated with paclitaxel or docetaxel and platinum-based regimens and almost 65% had clinical responses ([11,12] and data not shown); however, none in the present study had prior exposure to gemcitabine or vinorelbine. The RR of 22.5% in our study essentially replicates the 18% RR observed in the study of Hainsworth and colleagues [17]. One recent phase II study evaluating the weekly gemcitabine/vinorelbine regimen in patients with untreated or previously-treated NSCLC revealed that the RR in first-line was 42%, while it was 12% when the combination was applied in second-line treatment [18].

The individual contribution of each of these two cytotoxic agents; gemcitabine and vinorelbine, to the activity of the regimen after failure of first-line taxane + platinum-based treatment cannot reliably be discerned. Several studies have evaluated gemcitabine in patients failing prior platinum-based regimens yielding RRs ranging from 3 to 25% [7–9,19,20]. The most impressive results with single-agent gemcitabine were reported by Crino and colleagues [9]; a 19% RR and a 1-year actuarial survival of 45% in a group of patients that had failed prior platinum-based therapy, while only 15% of these had taxane + platinum-based combinations [9]. Therefore, it can be said that the majority of their patients had suboptimal therapy by today's standards, which might explain the 45% 1-year survival. A RR of 21% with no 1-year survival data (too early) was reported in another phase II study of single-agent gemcitabine treatment of 24 patients that had failed prior to paclitaxel + carboplatin regimens [8]. However, an extremely poor RR of 3% was reported in another study of similar design [7], thus, pointing to the notion that the differences in the observed RRs and survival figures might be the result of varying definitions of resistance to prior therapy and the inclusion of variable numbers of patients in these studies having more indolent or less disseminated disease at relapse.

While vinorelbine has established activity as a single-agent and in combination with cisplatin in first-line treatment of advanced NSCLC [2,21], the results obtained in second-line treatment with vinorelbine monotherapy have, in general, been poor. One recent randomised three-arm study comparing single-agent docetaxel 100 or 75 mg/m^2/3 weeks versus vinorelbine

30 mg/m^2/week versus ifosfamide 6 g/m^2 (divided over 3 days)/3 weeks in platinum-pretreated patients with relapsed NSCLC demonstrated no responses among 122 patients allocated to the single-agent vinorelbine arm [10]. However, there was no limit in this study on the number of prior chemotherapy regimens and most patients might had been heavily pretreated. Additionally, no responses were documented in two other phase II studies of vinorelbine in platinum-refractory NSCLC [22,23]. Therefore, it cannot be ruled out that the activity observed in the present and previous [17,18] phase II studies evaluating the gemcitabine/vinorelbine combination at second-line might be attributed to gemcitabine alone.

Both gemcitabine and vinorelbine, when administered as single agents, have demonstrated an improvement in quality of life over BSC alone, while vinorelbine has also resulted in a prolongation of survival in randomised phase III trials concerning chemonaive patients with advanced NSCLC [24,25]. However, to date, considering all of the newer agents, only docetaxel has demonstrated reproducible activity [6] and proven value over BSC in randomised phase III trials in the setting of relapsed/refractory NSCLC [1]. Therefore, randomised trials of the gemcitabine/vinorelbine regimen versus single-agent gemcitabine versus BSC will be warranted before recommending the combination as a standard non-toxic second-line treatment in taxane + platinum-pretreated NSCLC.

Recent phase I/II studies have demonstrated substantial activity of the weekly gemcitabine/vinorelbine combination administered in chemotherapy-naïve patients with stage IIIB/IV NSCLC [26–30]. Objective RRs ranged from 25 to 40%, median overall survival (OS) from 8 to 12.5 months and 1-year survival 33–48%. Both days 1 + 8 (every 3 weeks) and days 1 + 8 + 15 (every 4 weeks) weekly schedules were applied and the most convenient and less toxic proved to be the days 1 + 8/3 week regimens. Another phase I study evaluating ifosfamide added to the gemcitabine/vinorelbine combination demonstrated an encouraging 50% RR, equivalent to the current cisplatin-based regimens, in chemotherapy-naïve patients with advanced NSCLC [31].

Given the excellent tolerability and reduced toxicity of the gemcitabine/vinorelbine regimen, a recent phase III study of the Southern Italian Cooperative Oncology Group in elderly or unfit patients with advanced chemotherapy-naïve NSCLC evaluated single-agent vinorelbine versus gemcitabine/vinorelbine. In the final analysis of this trial, gemcitabine/vinorelbine proved superior to single-agent vinorelbine in terms of RR, quality of life improvement, and median survival [32].

In this study of tanxane + platinum-pretreated NSCLC patients, the combination of gemcitabine and vinorelbine was found to be very tolerable as regards toxicity, as had been the case in the study of Hainsworth and colleagues [17]. No cases of febrile neutropenia or grade 4 thrombocytopenia were encountered in our study compared with 7 and 2% incidences for these toxicities, respectively, reported by Hainsworth and colleagues [17]. It is our opinion that the days 1 and 8 (3-weekly) schedule, used in our study, is even less toxic than the days 1, 8 and 15 (4-weekly) schedule of drug administration and given the results of other first- or second-line studies, it is expected that the former (days 1 and 8 gemcitabine/vinorelbine) regimen might form the basis for future phase II or phase III studies in relapsed NSCLC. Moreover, the lack of significant alopecia represents another major advantage of the regimen in terms of acceptance by patients exposed to prior more toxic taxane-containing regimens.

Given the meaningful activity, low toxicity and tolerability of the gemcitabine/vinorelbine combination evaluated in the present study in taxane + platinum-pretreated patients with NSCLC, which essentially confirmed the observations raised with the same combination in a recent multicentre phase II study [17], this should stimulate interest in evaluating the combination against BSC, single-agent gemcitabine or docetaxel in order to define the optimal second-line treatment.

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