Cancer Chemother Pharmacol (2015) 75:821–827
DOI 10.1007/s00280-015-2707-x

ORIGINAL ARTICLE

Cisplatin in combination with metronomic vinorelbine as front-line treatment in advanced non-small cell lung cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG)

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Received: 1 December 2014 / Accepted: 13 February 2015 / Published online: 22 February 2015

Abstract
Purpose To evaluate the safety and efficacy of metronomic vinorelbine in combination with cisplatin as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC).
Patients and methods A total of 41 patients with inoperable stage IIIb or stage IV NSCLC (14 with adenocarcinomas, 19 with squamous cell carcinoma and eight with other types), PS = 0–2, were treated with cisplatin (80 mg/m^2) in combination with oral metronomic vinorelbine (60 mg total dose, every other day) in cycles of 21 days.
Results A total of 35 patients who received at least one cycle of chemotherapy were evaluable for toxicity and response. Partial response was achieved in 13 patients (ORR 37.1 %; CI 21.1–53.1 %) and stable disease in 10 (28.6 %). After a median follow-up period of 26.2 months (range 0.5–33.4 months), the median progression-free survival was 4.2 months and the median overall survival 12.0 months. The 1-year survival rate was 52.6 %. Myelosuppression was the main adverse event with grade 3 and 4 neutropenia occurring in five (14.3 %) and six (17.1 %) patients, respectively. Three of these patients presented with febrile neutropenia and there was one death due to sepsis. Non-hematologic toxicities were mild.
Conclusion Cisplatin in combination with metronomic vinorelbine is an active, although myelotoxic, therapeutic option in the first-line setting for the treatment of patients with locally advanced and metastatic non-small cell lung cancer, which merits further evaluation in randomized trials.

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Keywords Non-small cell lung cancer · Metronomic · Vinorelbine · Cisplatin

Introduction

Lung cancer is the leading cause of cancer deaths worldwide [1]. It is estimated that in 2012, 1,800,000 new cases of lung cancer occurred worldwide and caused almost 1,600,000 deaths [2]. Although its incidence during the last years declines over men, it increases among women; in addition, since 1990, the mortality in women from lung cancer has reached the mortality of breast cancer [3].

There is clear evidence from several prospective trials and meta-analyses that chemotherapy offers a statistically significant advantage in terms of overall survival (OS) and quality of life (QoL) compared to best supportive care in patients with advanced non-small cell cancer (NSCLC) [4]. Platinum-based chemotherapy doublets have improved the clinical outcome in NSCLC by producing 1-year survival rates of 30–40 % and are considered as the cornerstone of treatment for these patients. Current clinical practice is strongly directed by tumor histology with the combination of cisplatin/gemcitabine to be mainly used for the treatment of squamous cell lung carcinoma and the combination of pemetrexed/carboplatin or cisplatin (±bevacizumab) for adenocarcinomas [5]. Despite the advances on systemic cytotoxic chemotherapy of advanced NSCLC during the last decade, especially in non-squamous histology, there is no platinum-based regimen, which has shown superiority in terms of toxicity and efficacy [6].

The prognosis for advanced inoperable NSCLC, especially in cases lacking 'drugable' driver mutations, remains poor. Initial preclinical studies conducted in mice have shown that administration of the various chemotherapeutic

agents at the maximum tolerated dose levels has yielded the higher cure rate [7]. Thus, in chemotherapy regimens, the drugs are administered at their maximum tolerated doses resulting to higher incidence of adverse events (AEs). As a consequence, dose reductions are required which may impair the efficacy of anticancer treatments. In addition, adverse events due to high drug dosages often require an extended intra-cycle period of rest [8], which may result of tumor regrowth and selection of clones which could be resistant to therapy. Moreover, these time intervals allow recovery of tumor angiogenesis since neo-vascular endothelial cells had time for regrowth and, eventually, led to repopulation of tumor bed by proliferating cancer cells [8].

Continuous 'stimulus' of cancer cells and proliferating tumor endothelial cells by frequent administration at lower doses of a particular chemotherapeutic agent (a tenth to a third of the maximum tolerated dose) is known as metronomic therapy, which has been shown to provide sustainable clinical responses [9]. Metronomic therapy seems to exert an anti-angiogenic effect by inducing apoptosis of vascular endothelial cells [10]. Unlike dose-dense chemotherapy, which mainly targets dividing tumor cells, metronomic treatment targets, primarily, the neo-vascular endothelial cells surrounding tumor cells [11]. In addition, metronomic chemotherapy has been proposed to restore the normal immunity by increasing the number and the function of lymphocytes and decreasing the number of circulating immunosuppressive Tregs [12]. Moreover, the administration of 'continuous', low-dose, metronomic chemotherapy promotes the maturation of dendritic cells [13] resulting, thus, to modulation of immune response.

Vinorelbine is the first agent to demonstrate a survival benefit, when combined with cisplatin in the adjuvant setting of NSCLC [14]. In addition, vinorelbine-based regimens have also been proved active in the treatment of advanced NSCLC while an anti-angiogenic efficacy has also been documented [15]. The promising results of a phase I study conducted by our group, which demonstrated 20.7 % objectives responses in patients with metastatic NSCLC, led to the design of this current phase II study [16]. Its rationale is to combine the two different strategies of high and active dose of cisplatin with the metronomic administration of vinorelbine, in patients with NSCLC, in an attempt to maximize the clinical benefit.

Patients and methods

Patient eligibility

Chemotherapy-naïve patients with histologically or cytologically confirmed inoperable locally advanced (stage IIIb with supraclavicular lymph node metastasis), recurrent or metastatic (stage IV) NSCLC were enrolled in the study. Additional inclusion criteria were: age >18 years old; ECOG performance status (PS) of 0–2; bi-dimensional measurable disease; adequate bone marrow (hemoglobin >9.5 g/dl, absolute neutrophil count >1500/dl, platelet count >100,000/dl), liver [prothrombin time international normalized ratio (INR) <1.5 times the upper normal limit (UNL)] and renal function (serum creatinine <2 mg/dl); life expectancy of at least 3 months and written informed consent. Exclusion criteria included: a mixed NSCLC and small cell tumors; prior systemic therapy for advanced disease; bleeding diathesis or coagulopathy; clinically significant cardiovascular disease or myocardial infarction within the last 6 months; active infection; pregnancy and lactation as well as psychiatric disorders. Concerning EGFR status, all patients were EGFR wild type. Regarding ALK, the majority of the patients were recruited in 2010, when no test for detection EML-ALK fusion gene rearrangement was officially approved. The study obtained approval by the Ethics and Scientific Committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices guidelines.

Patient evaluation

Pre-treatment evaluation included a complete medical history, physical examination and blood pressure measurement; a complete blood count (CBC) with differential and platelet count; standard biochemical profile; electrocardiogram (ECG); chest X-rays; computed tomography scans of the chest, abdomen and brain as well as bone scintigraphy. During treatment, a CBC count was performed weekly; in case of grade 3 and 4 neutropenia and thrombocytopenia, the CBC count was performed daily until neutrophil count was more than 1000/dl and platelets more than 50,000/dl. A detailed medical history was taken, and complete physical examination was performed before each course of treatment to document symptoms of disease and chemotherapy-related toxicities. Biochemical tests, blood measurement, ECG and chest X-rays were performed every 3 weeks. Lesions assessable by ultrasound and/or computed tomography scans were evaluated after every two courses of treatment using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [17].

Treatment

Vinorelbine (Navelbine; Pierre Fabre, Toulouse, France) was given at the dose of 60 mg (flat dose) orally every other day (Monday, Wednesday and Friday) continuously. Cisplatin was given at the dose of 80 mg/m^2 over 1-h infusion on day 1 after adequate hydration, every 3 weeks. These

doses were defined in a previous phase I study conducted in our center [16]. Treatment was scheduled to be given for up to four cycles. If objective response or disease stabilization was documented, two additional cycles could be administered upon physician decision. Maintenance metronomic administration of vinorelbine was allowed after 4–6 chemotherapy cycles until disease progression, intolerable toxicity or patients' request. Dose-adjustment criteria were based on hematologic parameters. Doses of both drugs were reduced by 20 % in the subsequent cycle in case of febrile neutropenia or grade 4 neutropenia or thrombocytopenia lasting for more than 5 days; in the absence of fever, all drugs were reduced by 15 % in the subsequent cycles if the absolute granulocyte count was less than 500/dl and platelets count less than 75,000/dl. A one-week treatment delay and/or a 20 % dose reduction in vinorelbine and cisplatin were performed in patients with >grade 2, non-hematologic toxicity. Dose reductions were maintained for all subsequent treatment cycles. Toxicity was graded according to the NCI-Common Terminology Criteria for adverse events (NCTCAE: version 3.0). Prophylactic administration of rhG-CSF was not allowed.

Statistical design

This is an open-label, single-arm, multicenter phase II trial, which was conducted in nine Greek centers. The primary end point of the study was the objective response rate (ORR) and the secondary end points were progression-free survival (PFS), overall survival (OS) and toxicity assessment. The sample size calculation was based on the ORR. According to the Simon's two-stage min–max design, assuming that the expected ORR will be at 35 % (based on historical data) and the minimum acceptable response rate at 18 %, a minimum of four responses were required among the first 22 enrolled patients in order to continue to the second part of the trial. A total of 41 patients had to be enrolled in the trial; treatment would be declared sufficiently promising if at least 12 (ORR 29.3 %) responses were observed. The probability of accepting a treatment with a real response rate of less than or equal to 18 % would be 5 %. On the other hand, the risk of rejecting the treatment with a response rate of at least 35 % will be 20 %.

All patients who received at least one cycle of treatment were evaluable for analysis. OS and PFS were calculated from the date of randomization until the date of death and the date of documentation of disease progression, respectively, and were estimated using the Kaplan–Meier method. Qualitative variables were compared to the use of Chi-squared test. A $p < 0.05$ considered to indicate statistical significance. Continuous variables are summarized in frequency tables. Survival data are presented with 95 % CI.

Table 1 Patient characteristics

Characteristic	*n*	%
Age		
Median (min–max)	64 (49–80)	
Sex		
Male	35	85.4
Female	6	14.6
Performance status (ECOG)		
0	26	63.4
1	15	36.6
Stage		
IIIb	12	29.3
IV	29	70.7
Histology		
Squamous	19	46.3
Adenocarcinoma	14	34.1
Mixed	1	2.4
Large cell	3	7.3
Undifferentiated	4	9.8
Previous treatments		
Surgery	6	14.6
Consolidation RT	1	2.4
Curative RT	1	2.4
Palliative RT	4	9.8

ECOG Eastern Cooperative Oncology Group, *RT* radiotherapy treatment

Results

Patients' characteristics

From May 2010 to May 2014, a total of 41 patients were enrolled in the study. The patients' median age was 64 years (median 49–80), 35 (85.4 %) were men, all had an ECOG PS of 0–1 and 29 (70.7 %) stage IV disease; histology was squamous cell in 19 (46.3 %) patients and adenocarcinoma in 14 (34.1 %), one patient had mixed histology (adenosquamous) (2.4 %), three large cell (7.3 %) and finally four undifferentiated type (9.8 %). Among them, four patients had received prior palliative irradiation (two patients for CNS and four for bone metastases), whereas six patients had undergone prior surgery for localized disease. Demographic and baseline patients' characteristics are listed in Table 1.

Compliance with treatment

A total of 162 chemotherapy cycles were administered with a median of four cycles/patient (range 1–6). Dose reduction was required in 28 cycles (17.3 %), because of hematologic ($n = 22$ cycles), non-hematologic ($n = 3$ cycles), both

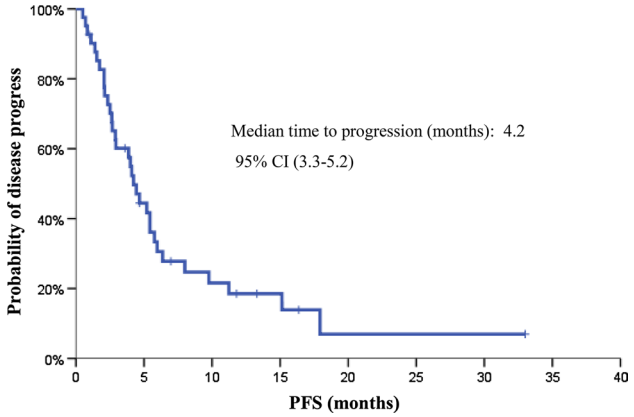

Fig. 1 Kaplan–Meier *curve* for progression-free survival estimate

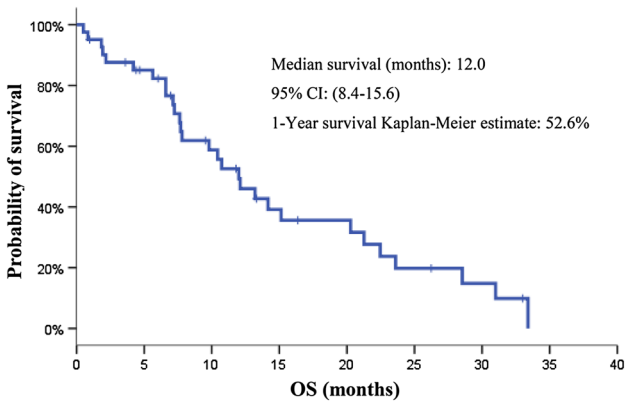

Fig. 2 Kaplan–Meier *curve* for overall survival estimate

hematologic and non-hematologic toxicity ($n = 1$ cycle) and physician's decision ($n = 2$ cycles). Twenty-one cycles (13.0 %) were delayed for the following reasons: patients' request unrelated to treatment or disease ($n = 7$ cycles), hematologic ($n = 13$ cycles) and non-hematologic ($n = 1$ cycle) toxicity. At the time of analysis, among the 35 treated patients, 13 patients discontinued treatment after completion as per protocol, 17 due to disease progression and five because of treatment-related adverse events (among them one toxic death). Vinorelbine dosage was reduced in 13 patients (32 %, range 30–50 mg) and cisplatin in three patients, respectively (7.3 %). The mean dose intensity for vinorelbine was 170 mg/week (range 92.4–170 mg/week), for CDDP 26.3 mg/m^2/week (range 15–26.7 mg/m^2/week) corresponding to the 94.4 and 98.5 % of the protocol predicted dose, respectively.

Efficacy

A total of 35 patients were evaluable for response. Three patients were non-evaluable for response since they did not receive treatment, because during the pre-treatment period presented with cerebral stroke ($n = 1$ patient), massive hemoptysis requiring palliative radiotherapy ($n = 1$ patient) and rapid deterioration of performance status ($n = 2$ patients). Finally, two patients withdrew consent ($n = 2$ patients).

There was no patient who experienced complete response (CR). Partial response (PR) was documented in 13 patients (37.1 %; 95 % CI 21.1–53.1 %), stable disease (SD) in 10 (28.6 %) and disease progression in 12 (34.3 %). The disease control rate (PR + SD) was 65.7 %. There was no correlation between the response rate, the patients' performance status or the stage of the disease. With a median follow-up period of 26.2 months (range 0.5–33.4 months), the median PFS was 4.2 months (95 % CI 3.3–5.2) (Fig. 1). At the time of analysis, 29 (70.7 %) patients had died. The reasons of death were disease progression ($n = 27$), treatment-related toxicity (sepsis due to febrile neutropenia; $n = 1$ patient) and one death due to sepsis unrelated to treatment. The median OS was 12 months (95 % CI 8.4–15.6) (Fig. 2), and the 1-year survival estimate was 52.6 %.

Safety

All patients who received at least one cycle of chemotherapy were evaluable for toxicity. Most of them (77.1 %) reported only mild adverse events (grade 1–2). Grade 3–4 neutropenia and thrombocytopenia occurred in 31.3 and 2.9 % of the patients, respectively. Hospitalization for intravenous administration of antibiotics and recombinant G-CSF support was required for three patients who developed febrile neutropenia; one of these patients died, whereas the other two recovered uneventfully. The most common grade 3 and 4 non-hematologic toxicity was fatigue, occurring in 11.5 % of the patients (Table 2).

Discussion

Non-small cell lung cancer is a highly lethal, malignant disease exhibiting short survival times in the advanced stages. Improving the treatment for inoperable, locally advanced and metastatic NSCLC is considered challenging. Meta-analyses based on clinical trials conducted in the era before targeted treatment and driver mutation testing (e.g., EGFR, EML-ALK fusion gene) were available, which demonstrated that chemotherapy was associated with an improved overall survival (OS), irrespectively of histologic type, age, gender and performance status (PS) compared to best supportive care [4]. Moreover, the cisplatin-based chemotherapeutic regimens improved the 1-year survival rate at 35 % compared to 30 % with single agent [18].

Table 2 Adverse events related to study

	GrI		GrII		GrIII		GrIV	
	n	%	*n*	%	*n*	%	*n*	%
Leukopenia	4	11.4	4	11.4	2	5.7	4	11.4
Neutropenia	3	8.6	5	14.2	5	14.2	6	17.1
Febrile neutropenia	–	–	–	–	–	–	3	8.6
Anemia	21	60.0	9	25.7	–	–	–	–
Thrombocytopenia	5	14.3	–	–	1	2.9	–	–
Nausea	2	5.7	2	5.7	–	–	–	–
Vomiting	1	2.9	3	8.6	–	–	–	–
Constipation	1	2.9	1	2.9	–	–	–	–
Fatigue	4	11.4	5	14.2	3	8.6	1	2.9

During the last years, the concept of metronomic therapy has gained the interest of the oncologists based on its biological mechanism of action, as mentioned above [11]. Metronomic therapy seems to be better tolerated, whereas it can induce prolonged tumor control, even in patients with poor performance status [19]. The proposed mechanism of action is very attractive [20, 21], since it may exert an anti-angiogenic effect by impairing different pathways of angiogenesis of these reported for the anti-angiogenic inhibitors which blockade the VEGF/VEGFR axis. In addition, its ability to restore the function of the immune cells makes it a particularly interesting therapeutic approach.

In the current study, we sought to evaluate a new treatment paradigm by combining the standard doses of cisplatin with vinorelbine given with a metronomic schedule. The regimen had expected and manageable toxicity profile as it was already observed in the initial phase I study conducted by our group [16]. Indeed, the three-fourths of the enrolled patients did not experience severe toxicity greater than grade 2. However, we need to stress that the regimen is myelotoxic since almost 31.3 % of the patients developed grade 3 and 4 neutropenia, three patients developed febrile neutropenia and one patient died because of sepsis. These findings imply that the regimen should be administered with caution and close monitoring of the hematologic toxicity. Conversely, the main severe non-hematologic toxicity was fatigue. The current multicenter study demonstrated that the combination of cisplatin with metronomic vinorelbine met its primary end point, which was the overall response rate. Indeed, the regimen resulted in an ORR of 37.1 % (disease control rate of 65.7 %) and a median PFS of 4.2 months. In addition, the regimen resulted in a median OS of 12 months and at a 1-year survival rate of 52.6 %. These efficacy results are favorably comparable with those achieved with other chemotherapy regimens, which are associated with a less favorable toxicity profile [22].

So far, the unique anti-angiogenic agent approved for the treatment of NSCLC is bevacizumab [23–25]. Bevacizumab is indicated for patients with good performance status and non-squamous histology and its addition to platinum-based doublets and its continuation as maintenance treatment have demonstrated an improvement in clinical efficacy (in terms of ORR, PFS and OS) compared to chemotherapy alone. However, the administration of bevacizumab has been implicated with severe and lethal, sometimes, adverse events such as hypertension, bleeding and/or thrombosis and bowel perforation [26]. Furthermore, the risk of severe toxicity (e.g., thromboembolic events, hemoptysis) from regimens including bevacizumab may be increased in elderly patients [27]. A recent retrospective cohort study reported that bevacizumab in combination with carboplatin/paclitaxel in elderly patients (older than 65 years old) does not offer any survival benefit [28]. Bearing in mind those limitations in the use of bevacizumab, the addition of metronomic vinorelbine to cisplatin in continuous, low-dose schedule could be considered as a viable option in patients with locally advanced or metastatic NSCLC, especially in subgroups of patients such as elderly or with squamous cell histology, where the treatment options are more limited. Finally, we should also take into consideration that compared to i.v. vinorelbine and other antineoplastic agents, oral vinorelbine has demonstrated a cost-saving advantage [29].

In conclusion, the results of the current study demonstrated that the cisplatin/metronomic vinorelbine combination is an active chemotherapeutic regimen against locally advanced or metastatic NSCLC. Despite its myelotoxicity, the toxicity profile of the regimen was tolerable and overall well manageable. The aim of the current study was to introduce a new paradigm in oncology therapies by combining the indisputable effect of cisplatin with metronomic administration of vinorelbine. Indeed, we consider that the results were notably promising and this regimen could be reserved

for those patients who are not able to receive the indicated conventional treatment.

Acknowledgments This work was partially supported by a research grant from the Cretan Association for Biomedical Research (CABR).

Conflict of interest The authors declare that they have no conflict of interest.

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