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Triplet Chemotherapy with Docetaxel, Gemcitabine and Liposomal Doxorubicin, Supported with Subcutaneous Amifostine and Hemopoietic Growth Factors, in Advanced Non-small Cell Lung Cancer

GEORGE PATLAKAS, DEMOSTHENES BOUROS,
SOFIA TSANTEKIDOU-POZOVA and MICHAEL I. KOUKOURAKIS

Departments of Pneumonology and Radiotherapy-Oncology,
Democritus University of Thrace, Alexandroupolis, Greece

Abstract. *The activity of a triplet of chemotherapeutic drugs, namely docetaxel, gemcitabine and liposomal doxorubicin, was investigated in patients with advanced non-small cell lung cancer. The regimen was supported with amifostine cytoprotection (1000mg injected subcutaneously) and hemopoietic growth factors (rhuG-CSF and rhuEPO) in an attempt to minimize the substantial toxicity reported in previous studies investigating docetaxel/gemcitabine chemotherapy. Twenty chemotherapy- naïve patients with advanced non-small cell lung cancer (NSCLC) (18 with stage IV and 2 with stage IIIb) were recruited. None of the patients presented with grade 3-4 hematological or non-hematological toxicity. Palmar-plantar erythrodysesthesia grade 2 was noted in 6/20 (30%), mucositis/oesophagitis grade 2 in 3/20 (15%) and mild alopecia in 6/20 (30%) patients. No case of interstitial pneumonia was noted. The overall response rate (complete and partial) in 18 evaluable patients was 33% (6/18), with 1/18 (5%) patients achieving complete response. The median survival was 11 months. The efficacy of the regimen was as high as the one reported in gemcitabine/docetaxel studies, but the toxicity was remarkably lower. Amifostine may have contributed to the better tolerance profile observed.*

Metastatic non-small cell lung cancer (NSCLC) is an incurable disease. Several randomized studies have shown that chemotherapy offers a small but still significant survival advantage (1-3), which encourages the conduct of clinical trials aiming to establish more effective regimens. Although cis-platinum-based regimens are considered to bear the highest activity, a recent randomized trial showed that chemotherapy based on two novel drugs, namely docetaxel and gemcitabine, is equally effective and less toxic, though still with substantial toxicity (4-7). As the performance status of these patients is already affected at the time of diagnosis and their life expectancy is no more than several months, it is of importance to use easily administered regimens on an outpatient basis, as well as to minimize the chemotherapy toxicity, thus protecting the quality of life.

In the present study, we investigated the activity of a triplet of chemotherapeutic drugs, namely docetaxel, gemcitabine and liposomal doxorubicin, in patients with advanced NSCLC. The addition of liposomal doxorubicin, a drug that is preferentially accumulated into the tumor environment (8), could eventually enhance the good activity reported for the docetaxel/gemcitabine doublet. The triplet was supported with amifostine cytoprotection and hemopoietic growth factors (granulocyte-colony stimulating factor/G-CSF and human erythropoietin/HuEPO) in an attempt to minimize the substantial toxicity reported in previous studies investigating docetaxel/gemcitabine chemotherapy.

Patients and Methods

Recruitment criteria. Twenty chemotherapy-naïve patients with histologically confirmed advanced NSCLC were recruited in this study (from 2001-2002) to evaluate the tolerance and activity of a triplet combination chemotherapy of docetaxel, gemcitabine and liposomal doxorubicin. The study was an 'in-house' and not a company sponsored trial. The exclusion criteria, also valid for the recruitment of patients in the chemotherapy protocol, were the following: white blood cells (WBC) <2,500/μl, platelets (Pt) <120,000/μl and creatinine

Correspondence to: Michael I. Koukourakis, MD, Department of Radiotherapy – Oncology, PO BOX 12, Alexandroupolis 68100, Greece. Tel: +30-25510-74622 Fax: +30-25510-30349, e-mail: targ@her.forthnet.gr

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Table I. *Patient characteristics.*

Total No. of patients	20
Male:Female	18:2
Age, years	
median	62
range	46-78
WHO PS	
Median	1
Range	0-2
Tumor type	
Squamous	11
Adenocarcinoma	7
Large cell	2
Stage	
IIIb inoperable	1
IIIb operated*	1
IV	18
Previous chemotherapy	
Yes	0
No	20

* positive margins

clearance <55ml/min. Patients with hemoglobin (Hb) <10g/dl were transfused until Hb levels rose >11g/dl. Pregnant women or patients with major heart, lung, liver, renal dysfunction, psychiatric disease or hematological malignancies were excluded. The median age of our patients was 62 years (range 46-78). The patients' characteristics are shown in Table I.

Pretreatment and treatment evaluation. Baseline studies included physical examination, whole blood count (WBC) with differential and platelet count, complete biochemical profile and computed tomography of the chest and upper abdomen. Patients were followed with WBC, serum urea and creatinine and liver enzymes once a week. The WHO scale was used to assess chemotherapy toxicity.

Response to treatment was assessed with CT-scan performed 2 weeks following the delivery of 6 cycles (3 months) of the regimen. CR was defined as disappearance of the measurable lesion, whilst partial and minimal response refers to 50-95% and 25-49% reduction of tumor dimensions, respectively. Small reductions of tumor dimensions between 0-24%, lasting for at least 2 months after response documentation, were considered as stable disease. All other cases were considered as progressive disease.

Chemotherapy regimen. All three drugs were given at a two-week interval. Docetaxel (Taxotere®) was given at a dose of 50mg/m^2, gemcitabine (Gemzar®) at a dose of 1000mg/m^2 and liposome doxorubicin (Caelyx®) at a dose of 20mg/m^2.

Table II. *Hematological, non-hematological toxicity*

	Grade 0/1	Grade 2	Grade 3/4
Asthenia	18	2	0
Alopecia	14	6	0
Erythrodysesthesia	14	6	0
Fever	18	2	0
Oesophagitis	19	1	0
Stomatitis	18	2	0
Fungal infection	20	0	0
Pneumonitis	20	0	0
Hypotenstion	20	0	0
Fluid retention	20	0	0
Pleural effusion	20	0	0
Neurosensory	20	0	0
Neutropenia	18	2	0
Hemoglobin	19	1	0
Platelets	19	1	0
Hypersensitivity	20	0	0

Table III. *Response rate according to histology.*

Histology	No. pts*	CR(%)	PR(%)	MR(%)	SD	PgD
Squamous	9	0 (0)	3 (33.4)	2 (22.2)	0 (0)	3 (33.4)
Adenocarcinoma	7	1 (14.5)	1 (14.5)	0 (0)	2 (28.5)	3 (42.5)
Large cell	2	0 (0)	1 (50)	0 (0)	1 (50)	0 (0)
All cases	18	1 (5.6)	5 (27.4)	2 (11.2)	4 (22.3)	6 (33.5)

*Two patients had no measurable disease

No premedication was used and the regimen was delivered on an outpatient basis. Methyl-prednizolone 250mg diluted in 50ml normal saline (NS) was infused within 5 minutes. Tropisetron (10mg *i.v.*) was given as antiemetic treatment. Immediately afterwards, amifostine (Ethyol®) 1000mg flat dose diluted in 5ml NS was injected subcutaneously in the two shoulders of the patients (2.5ml in each). Patients were kept in a sitting position with continuous blood pressure monitoring. Docetaxel was diluted in 250ml normal saline and infused within 30 minutes. Subsequently, gemcitabine, diluted in 250ml NS, was infused within 30 minutes Caelyx® was diluted in 250ml dextrose water and injected within 30 minutes. No steroids were used thereafter.

G-CSF (Granulokine®) was given prophylactically from the beginning of treatment. Thee hundred and eighty μg were injected subcutaneously for 4 consecutive days, starting on day 4 of each cycle. Erythropoietin (Eprex®) was also given prophylactically at a dose of 40,000 IU once a week (days 4 and 11). We chose to administer hemopoietic growth factors despite the administration of amifostine, in order to achieve maximum cytoprotection against

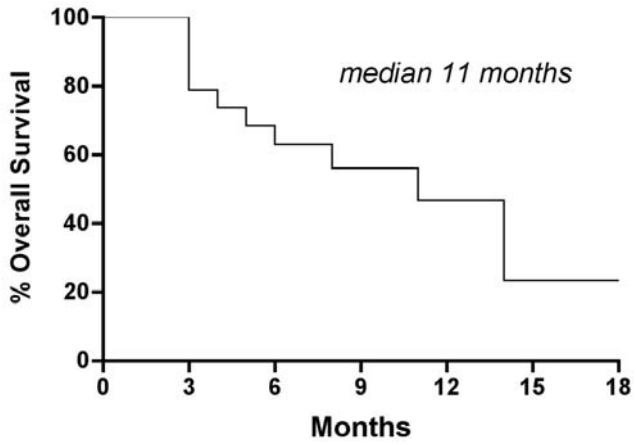

Figure 1. *Overall disease-specific survival in advanced NSCLC treated with docetaxel, gemcitabine and liposomal doxorubicin.*

hematological toxicity, which is quite high after gemcitabine/docetaxel chemotherapy (4-7).

Treatment adjustments. Any grade 3/4 toxicity related to chemotherapy was followed by treatment interruption for one week or more if necessary. When neutropenia grade 2 was confirmed at the time when the subsequent cycle was to be administered, the treatment was not interrupted but G-CSF was given for 6 consecutive days (instead of 4) starting on day 4 of the cycle.

Results

Chemotherapy tolerance. Table II reports the toxicity noted in patients. Overall the regimen was very well tolerated. No grade 3-4 hematological or non-hematological toxicity was noted. Palmar plantar erythrodysesthesia grade 2 was noted in 6/20 (30%) patients. Mucositis/oesophagitis grade 2 was also noted in 3/20 (15%) patients. Mild alopecia was quite common (6/20 grade 2). No case of interstitial pneumonia was noted.

Amifostine tolerance. Amifostine subcutaneous administration was never followed by hypotension. Mild nausea/vomiting grade 2 was noted in 4/20 (20%) of patients, while dizziness was frequent (10/20 patients). Fever-rash symptomatology or other systemic cutaneous reactions were not observed. Mild local erythema around the area of amifostine injection was noted in 5/20 (25%) patients, but this regressed within the following 2-3 days without treatment.

Response. Response to the regimen was assessed 2 weeks after the completion of 6 cycles of chemotherapy (3 months). In two patients, assessment of response was not feasible (one patient with stage IIIb disease and positive postoperative margins, and one with bone metastasis). Table III shows the treatment outcome according to the histology type. The overall response rate (complete and partial response) was 33% (6/18), with 1/18 (5%) patients achieving complete response. The median survival was 11 months (Figure 1).

Discussion

The combination of gemcitabine with docetaxel has been shown to be equivalent to and less toxic than platinum-based regimens in patients with NSCLC (7, 9). In a randomized trial, a high dose of gemcitabine (1000mg/m^2 twice every 3 weeks) and docetaxel (100mg/m^2 once every three weeks) was delivered, and the toxicity was not negligible (7). Grade 3-4 neutropenia and thrombocytopenia were noted in 22% and 5% of patients, respectively. The objective response rate reported was in the range of 30%, which is similar to the rate reported in phase II studies using a lower dose intensity of this doublet (10-12).

In a phase II study by Chen *et al.*, the combination of gemcitabine with docetaxel was feasible and provided promising response rates of 36% (10). The dose of docetaxel and gemcitabine was 30mg/m^2/weekly and 800mg/m^2/weekly twice every 3 weeks. High toxicity was, however, reported with 25% and 17% of patients experiencing grade 3-4 neutropenia and thrombocytopenia, respectively. Two out of 36 patients developed interstitial pneumonitis. A median survival of 7.1 months was reported. In a similar study, conducted by Popa *et al.*, a slightly higher dose of docetaxel (40mg/m^2/weekly) and gemcitabine (1000mg/m^2/weekly) was administered twice every 3 weeks (11). Again, grade 3-4 neutropenia and thrombocytopenia were noted in 19% and 7% of patients, respectively. Six patients (18%) developed interstitial pneumonia and fatigue was quite common (10/32). The complete and partial response rates were 3% and 21%, respectively. In a recent study by Niho *et al.*, the combination of docetaxel and gemcitabine produced 28% objective responses. The dose of docetaxel was standardised to 60mg/m^2 every three weeks and the dose of gemcitabine to 800mg/m^2/weekly twice every 3 weeks. Grade 4 neutropenia was noted in 18% of patients and grade 3 thrombocytopenia in 11% (12).

The dose intensity in the above phase II studies ranged between 3600-4000mg for gemcitabine and between 120-160mg/m^2 for docetaxel, every 6 weeks. In our study the dose intensity was 3000mg/m^2 and 150mg/m^2 every 6 weeks, for gemcitabine and docetaxel, respectively. In addition, a high dose of liposomal doxorubicin, near the maximum tolerated dose, was given, as the dose intensity was 60mg/m^2 every 6 weeks (13, 14). Liposomal doxorubicin is preferentially accumulated in the tumor environment (15, 16) and, in combination with docetaxel

and radiotherapy, produced a 30% complete response rate in patients with locally advanced NSCLC (17). We hypothesized that the addition of a potent DNA-damaging agent, selectively accumulating in the tumors, to the highly effective docetaxel/gemcitabine doublet, could further enhance the chemotherapy efficacy at the cost of augmentation of hematological and lung toxicity. The use of hemopoietic growth factors and of amifostine could contribute to the minimization of such toxicities. The present study aimed to investigate the validity of this hypothesis.

In contrast to the previous phase II studies, neutropenia or thrombocytopenia grade 3-4 were not observed in our study. G-CSF certainly was the main agent protecting patients from neutropenia, although the combination of G-CSF with amifostine may have also augmented the bone marrow activation. The negligible thrombocytopenia should be attributed to the cytoprotective efficacy of amifostine, the activity of which against platinum-induced thrombocytopenia is well established (18). Palmar plantar erythrodysesthesia was also minimal, which could be attributed to the split dose of liposomal doxorubicin and/or to amifostine protection. Interstitial pneumonia, previously reported to occur in 7-18% of patients receiving docetaxel/gemcitabine chemotherapy, was not observed in our series of patients, despite the addition of liposomal doxorubicin. Such an observation should be attributed to the cytoprotective efficacy of amifostine against lung damage. Indeed, several studies have confirmed the significant reduction of chemo-radiation-induced pneumonitis (19, 20).

The complete and partial response rate was 33% and the median survival 11 months, which is quite similar to those found in the previously reported phase II studies. The fact that the present regimen was less toxic compared to the doublet docetaxel/gemcitabine chemotherapy strongly suggests that G-CSF and amifostine support are essential to protect lung cancer patients receiving non-platinum regimens. Furthermore, the addition of liposomal doxorubicin did not increase toxicity. Whether the addition of liposomal doxorubicin to the doublet further enhances the responses and survival of metastatic NSCLC patients should be examined in randomized trials.

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