RESEARCH COMMUNICATION

Weekly Paclitaxel/ Docetaxel Combined with a Platinum in the Treatment of Advanced Non-Small Cell Lung Cancer: a Study on Efficacy, Safety and Pre-medication

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Abstract

Objectives: To evaluate the efficacy and safety of a weekly taxane schedule in the treatment of advanced non small cell lung cancers (NSCLCs) and to generate anoptimal pre-medication protocol for weekly taxane. Methods: From December 2001 to June 2006, 78 patients with advanced NSCLCs were recruited from the Department of Chemotherapy, Jiangsu Cancer Hospital and Research Institute. Paclitaxel was delivered at 80-100mg/m2 on days 1 and 8 (11cases), or 50-80mg/m^2 on days 1, 8 and 15 (23cases), while docetaxel was given with the same schedules at 35-45 mg/m^2 (30cases), or 25-35mg/m^2 (14cases). In all cases this was combined with a platinum-based drug (cisplatin, oxaliplatin or carboplatin) , followed by a 1 week rest. Four pre-medications were attempted were also compared. Results: All 78 patients received a total of 202 courses of treatment. Dose limiting toxicity was myelosuppression. Grades 3 and 4 leukopenia occurred in 19.2% (15/78). Of the 56 eligible patients who completed at least 2 courses, none had a complete response, 20 achieved a partial response and 5 showedprogression. Toxicity of pre-medications was indicated by: hypersensitivity (1 case), hypopotassemia (8 cases), myasthenia (5 cases), hiccups (1 case) and infection (2 cases). No treatment related deaths occurred. Conclusions: Weekly administration of paclitaxel /docetaxel is a safe and active protocol for advanced NSCLCs. Our recommendations for weekly pre-medication with taxane are: dexamethasone 2.25mg-7.5mg orally 12h and 2h before, promethazine and cimetidine 30min before paclitaxel; oral dexamethasone 4.5mg-7.5mg twice daily for three consecutive days (the day before, the day of, and the day after docetaxel), promethazine and cimetidine 30min before docetaxel.

Key Words: Non small cell lung cancer - Paclitaxel - Docetaxel - platinum chemotherapy -China

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Introduction

Approximately 75% of all lung cancers, a leading cause of cancer-related death worldwide, are of non-small cell lung cancer (NSCLC) type (Ferlay et al., 2001). Most patients in China present with locally advanced stage III or IV disease. Although current practice for treatment includes several newer generation agents such as vinorelbine, gemcitabine, paclitaxel or docetaxel with a platinum agent, no combination has yet emerged as a gold standard (Non-Small Cell Lung Cancer Collaborative Group,1995; Schiller et al., 2002). However, among the polychemotherapy schedules, paclitaxel or docetaxel plus cisplatin are considered standard treatments for advanced NSCLC in China (Chen et al., 2005). Paclitaxel blocks cancer cell cycling in the G2/M phase through inhibition of microtubular depolymerization, (Schif et al.,1979; Jordan et al.,1996) and may also induce apoptosis as well as inhibit angiogenesis (Belotti et al.,1996). Weekly chemotherapy has been extensively studied, especially with the taxanes (Akerley et al., 2003). Compared with 3-week dosage regimens, a weekly schedule of paclitaxel results in enhanced cytotoxicity, increases dose intensity and produces a favorable toxicity profile in NSCLCs (Fennelly et al.,1997; Seidman et al.,1998; Chang et al.,2001; Camps et al., 2006). To our knowledge, however, no standard pre-medication for weekly taxane has yet been established (Jatoi et al., 2003; Kaplan et al., 2004; Chen et al., 2005; Rui and San, 2005). The purpose of this study was thus to evaluate the efficacy and safety of weekly paclitaxel/docetaxel schedules for advanced NSCLC and to generate an optimal pre-medication protocol.

Materials and Methods

Patient selection

Seventy-eight patients with stage III or IV NSCLCs were recruited from the Department of Chemotherapy,

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Jiangsu Cancer Hospital and Research Institute from December 2001 to December 2005. All patients fulfilled the following criteria: older than 18 years, with complete medical records (including medical history, physical examination, complete blood cell count, and biochemical analysis profile), a computed tomographic (CT) scan of the tumor, and a whole-body radionuclide bone scan. Other clinical criteria were as follows: life expectancy >3 months, white blood cell count >4.0x10^9cells/L ,platelet count >100x10^9cells/L, hemoglobin level >100g/L, creatinine, aspartate aminotransferase/alanine aminotransferase, and total serum bilirubin levels not exceeding twice the normal upper limit, as well as a Karnofsky score≥60. The study protocol was approved by the ethics committee of Jiangsu Cancer Hospital and Research Institute.

Treatment plan

In our study four treatment protocols were attempted: a) Paclitaxel 80-100mg/m^2 by intravenous infusion(ivi) on days 1 and 8, combined with oxaliplatin 100-140mg/m^2 ivi on days 1 and 8 or cisplatin 15-20mg/m^2 ivi on days 1 to 5; b) Paclitaxel 50-80mg/m^2 ivi on days 1, 8 and 15, combined with cisplatin 15-20mg/m^2 ivi on days 1 to 5,or oxaliplatin 80-100mg/m^2 ivi on days 1, 8 and 15; c) Docetaxel 25-35mg/m^2 ivi on days 18 and 15 combined with cisplatin 20-30mg/m^2 ivi on days 1, 8 and 15, or oxaliplatin 50-70mg/m^2 ivi on days 1, 8 and 15, or carboplatin 40-50 mg/m^2 ivi on days 1, 8 and 15; d) Docetaxel 35-45 mg/m^2 ivi on days 1 and 8, combined with cisplatin 15-20mg/m^2 ivi on days 1 to 5, or oxaliplatin 50-70mg/m^2 ivi on days 1, 8 and 15. All were followed by a 1 week rest.

In this study four pre-medications protocols were also investigated: a) Dexamethasone administered intravenously 30 minutes before paclitaxel, at 40.0 mg, 10.0mg, or 7.5mg, then 50 mg of diphenhydramine and an H_2-blocker intravenously; b) Dexamethasone orally at 15mg, 12mg, 9mg or 4.5mg 12 hours and 2 hours, then 50 mg of diphenhydramine and an H_2-blocker intravenously 30 minutes before paclitaxel; c) Dexamethasone intravenously 30 minutes before docetaxel, at 40.0 mg, or 10.0mg, or 7.5mg and then 50 mg of diphenhydramine and an H_2-blocker intravenously; d) Dexamethasone orally at 7.5mg or 4.5mg twice a day for three consecutive days (the day before, the day of, and the day after docetaxel), then antihistaminic and an H_2-blocker 30 minutes before docetaxel.

Response and Toxicity Evaluation

Tumor size was determined by clinical examination and/or chest CT scan. The first assessment of response was performed after patients had completed 2 courses of chemotherapy. Complete blood cell counts and biochemical analyses were repeated weekly. Treatment response was recorded according to WHO criteria for chemotherapy efficacy assessment (Miller et al., 1981). A complete response was defined as the complete disappearance of all evidence of any tumor. Partial response was defined as ≥50% reduction in the sum of the products of the largest perpendicular diameters of all measured lesions for at least 4 weeks. Stable disease was defined as a decrease of <50% or an increase of <25% in well-outlined lesions for at least 4 weeks. Progressive disease was defined as an increase >25% in the cross-sectional area of one or more lesions, or the occurrence of new lesions. The National Cancer Institute Common Toxicity Criteria (version 2) were used to report and grade acute toxicity in this study.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. The male-to-female ratio was 2.4:1 and the median age was 56(range 28-79 years). Adenocarcinoma was the most common histologic subtype (59.0% of the total) and 61.4% of the patients had stage IV disease. Fourteen treated with paclitaxel (14/34) and 36 with docetaxel (36/44) had experienced prior chemotherapy. Approximately 69.2% of the patients had a Karnofsky score ≥80.

Treatment

Eleven patients were treated with paclitaxel 80-100mg/m^2 ivi on days 1 and 8 , 23 with paclitaxel 50-80mg/m^2 ivi on days 1, 8 and 15, 14 with docetaxel 25-35mg/m^2 ivi on days 1,8 and 15 and 30 with docetaxel 35-45 mg/m^2 ivi on days 1 and 8. As indicated in Table 2, 2 patients received 40.0 mg, 4 were given 10.0mg and 2 received 7.5mg of dexamethasone intravenously 30 minutes before paclitaxel. Two patients were given dexamethasone at 7.5mg, 12 at 6.0mg, 7 at 4.5mg, and 5 at 2.25mg orally 12 hours and 2 hours before paclitaxel. Nine patients received 40 mg, 4 were given 10.0mg and 7 received 7.5mg of dexamethasone intravenously 30 minutes before docetaxel. Twelve patients were administered dexamethasone 7.5mg and 12 were given 4.5mg twice orally for three consecutive days (the day before, the day of, and the day after docetaxel).

Response

Seventy-eight patients had a total of 202 courses of chemotherapy. Fifty-six (71.8%) received a minimum of 2 courses, and were eligible for further analysis of response: no patient had a complete response, 20 demonstrated a partial response, 31 remained stable and 5 showed progression. Among the 34 patients who entered in paclitaxel group, 6 received less than 2 courses of chemotherapy. The overall response rate for 28 evaluable patients was 32.1 %(9/28), including 9 with a partial response, 15 with stable disease and 4 exhibiting progression. For 44 patients treated with docetaxel, 28 patients received no less than 2 courses of chemotherapy: the overall response rate was 39.3 %(11/28), including 11 with a partial response, 16 with stable disease and one progression. The overall response rate for all 56 eligible patients was 35.7 %(20/56).

Toxicity

All 78 patients underwent toxicity assessment. Hematologic and nonhematologic evidence of toxicities of paclitaxel and docetaxel is summarizedin Table 3.

Table 1. Characteristics of Chinese Advanced Non-small Cell Lung Cancer Patients

Characteristic		Number	(%)
Age (years)	<60	41	52.6
	≥60	37	47.4
Sex	Male	55	70.5
	Female	23	29.5
Histology	Squamous cell cancer	26	33.3
	Adenocarcinoma	46	59.0
	Adenosquamous	4	5.1
	Undifferentiated	2	2.6
Stage	IIIA	11	14.1
	IIIB	17	21.8
	IV	50	64.1
Karnofsky score	60-69	6	7.7
	70-79	18	23.1
	80-89	36	46.2
	90-100	18	23.1

Twenty-six (34.0%) patients experienced grade 1-2, and 7 (9.0%) grade 3-4 anemia. Grade 3 and grade 4 leukopenia occurred in 19.2% (15/78). Nonhematologic toxicity was mild. the major symptom being alopecia, observed in 89.7%(70 /78) of patients. Grade 3 nausea and vomiting occurred in 7.7%. No treatment-related deaths occurred.

Pre-medication associated toxicity was also carefully monitored. Hypersensitivity occurred in 1 patient who had received 40mg dexamethasone intravenously for five to ten minutes before docetaxel. Eight patients experienced hypopotassemia(K^+=3.1±3.4mmol/L in 7 and K^+=2.4mmol/L in 1 patient) after either 40mg dexamethasone intravenously 30 minutes before paclitaxel (2 cases), 6mg/4.5 mg dexamethasone orally 12 hours and 2 hours before paclitaxel (3 cases), or 40mg dexamethasone intravenously 30 minutes before docetaxel (3 cases). However, their serum potassium values returned to normal after treatment. Myasthenia occurred with 40mg dexamethasone intravenously 30 minutes before paclitaxel (1 case), 6mg dexamethasone orally 12 hours and 2 hours before paclitaxel (1 case), and 40mg or 10mg dexamethasone intravenously 30 minutes before docetaxel (3 cases), the affected 5 patients reporting fatigue. Fluid retention was observed in two: one receiving 40mg dexamethasone intravenously 30 minutes before paclitaxel and another given 7.5mg dexamethasone twice a day orally for three consecutive days. Two patients experienced infection: one with 10mg dexamethasone intravenously 30 minutes before docetaxel, and another with 7.5mg dexamethasone intravenously 30 minutes before docetaxel. No pre-medication related deaths occurred.

Discussion

Weekly dosing of paclitaxel infusion has been demonstrated to be an effective and a well-tolerated schedule for NSCLC (Chang et al., 2001).In the present study of advanced NSCLC patients given weekly, low-dose combinations of paclitaxel with platinum, the overall response for all 28 evaluable patients was 32.1%. Based on this response rate, we conclude that these regimens confer modest control among Jiangsu Chinese patients

Table 2. Premedications for Weekly Taxane in Chinese Advanced Non-small Cell Lung Cancer Patients

Type	No. Patients	Taxane	Dexamethasone Total dose	Route
1*	2	paclitaxel	40.0 mg	intravenously
	4	paclitaxel	10.0 mg	intravenously
	2	paclitaxel	7.5 mg	intravenously
2*	2	paclitaxel	15.0 mg	orally
	12	paclitaxel	12.0 mg	orally
	7	paclitaxel	9.0 mg	orally
	5	paclitaxel	4.5 mg	orally
3*	9	docetaxel	40.0 mg	intravenously
	4	docetaxel	10.0 mg	intravenously
	7	docetaxel	7.5 mg	intravenously
4*	12	docetaxel	45.0 mg	orally
	12	docetaxel	27.0 mg	orally

Type 1* denotes: Dexamethasone administered intravenously 30 minutes before paclitaxel, at the following dose: 40.0 mg, 10.0mg, or 7.5mg. Type 2* denotes: Dexamethasone orally 12 hours and 2 hours before paclitaxel ,at the following dose: 7.5mg , 6mg, 4.5mg, or 2.25mg. Type 3* denotes: Dexamethasone intravenously 30 minutes before docetaxel, at the dosage of 40.0 mg, 10.0mg, or 7.5mg respectively.Type 4* denotes: Dexamethasone orally at 7.5mg or 4.5mg twice a day for three consecutive days (the day before, the day of, and the day after docetaxel)

Table 3. Hematologic and Non-hematologic Toxicity of Weekly Taxanes for Chinese Advanced Non-small Cell Lung Cancer Patients

Symptom	Toxicity Graded using NCI-CTC 1	2	3	4
Alopecia	69 (88.5)	1 (1.3)	0 (0.0)	0 (0.0)
Anemia	13 (16.7)	13 (16.7)	5 (6.4)	2 (2.6)
Leukopenia	12 (15.4)	20 (25.6)	12 (15.4)	3 (3.8)
Thrombocytopenia	5 (6.4)	10 (12.8)	5 (6.4)	1 (1.3)
Nausea/vomiting	13 (16.7)	8 (10.2)	6 (7.7)	0 (0.0)
Alopecia	69 (88.5)	1 (1.3)	0 (0.0)	0 (0.0)
Peripheric neuropathy	8 (10.3)	3 (3.8)	0 (0.0)	0 (0.0)
Hepatic impairment	5 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nephric impairment	4 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardic impairment	5 (6.4)	1 (1.3)	0 (0.0)	0 (0.0)

Data are Number (%); NCI-CTC, National Cancer Institute Common Toxicity Criteria version 2

with NSCLCs. Although comparisons across studies can be problematic, our response rate appears inferior to the 47.0% response rate reported by Chen et al. with a 3-week treatment schedule (Jatoi et al., 2003). Many studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelosuppression (Hainsworth et al.,1998; Briasoulis et al.,1999; Greco,1999). The overall response to weekly administration of docetaxel has been 31.6%-45% (Tsunoda et al., 2004; Kaira et al., 2005). Our figure for 28 patients, at 39.3% (11/28), was thus in line with the literature.

The patterns of toxicity observed in our study were quite similar to those reported earlier with paclitaxel / docetaxel and platinum combinations. Grade 3 and grade 4 leukopenia occurred in 19.2% (15/78). Twenty-six (33.3%) patients experienced grade 1-2 anemia, and 16.7% patients experienced grade 1 nausea/vomiting, probably reflecting intense antiemetic prophylaxis. The major non-hematology toxicity was alopecia. No

treatment-related death occurred. Incidence of neurotoxicity was also surprisingly low, considering that all agents cause neural damage, probably due to the low dose of paclitaxel given as a 3-hour infusion and docetaxel given as a 1-hour infusion. In this study, the toxicity encountered with weekly taxane pre-medications was also mild.

Whether the outcomes of weekly taxane pre-medications are more safe and effective, with more favorable toxicity profiles than other therapies requires confirmation with randomized trials.

In summary, weekly dosing of paclitaxel /docetaxel infusion appears to be a safe and active regimen for patients with advanced NSCLCs. Our recommendations for weekly taxane pre-medication are: dexamethasone 2.25-7.5mg orally 12h and 2h before, antihistaminic and an H2-blocker 30min before paclitaxel; dexamethasone 4.5-7.5mg twice a day orally for three consecutive days (the day before, the day of, and the day after docetaxel), antihistaminic and an H2-blocker 30min before docetaxel.

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