Docetaxel as Second-Line Chemotherapy for Advanced Non-Small Cell Lung Cancer

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Abstract

The purpose of this study was to evaluate the efficacy and safety of docetaxel as second-line chemotherapy for advanced non-small cell lung cancer (NSCLC). Thirty-four patients with advanced NSCLC received docetaxel 75 mg/m^2 (1-h intravenous infusion) every 3 weeks, with corticosteroid premedication. Of 28 evaluable cases, 18 were adenocarcinoma, 3 squamous cell, 3 large cell and 4 undifferentiated carcinoma. There were 16 male and 12 female patients with a median age of 55 (37-73) years and their median Karnofsky performance status was 70 per cent (60-90%). Five cases (19.2%) had liver metastases, 3 (11.5%) brain metastases, 6 (23%) bone metastases, and 17 (65.3%) metastatic nodules in the lung. Seventeen cases (50%) had received cisplatin-based and 12 (12/34, 35.3%) paclitaxel plus carboplatin prior to entering the present study. Besides chemotherapy, seven cases had received prior thoracic irradiation and two whole brain irradiation. Two cases had prior surgery for malignant pleural effusion and one had thoracotomy for the resection of the primary tumor. The time from the last dose of chemotherapy to the start of this study was less than 6 months in 20 cases, 6-12 months in 9, 12-24 months in 3 and more than 24 months in 2 cases. One patient with initial small cell lung cancer had developed NSCLC before entering this study. Three out of 28 cases achieved partial response (10.7%) and 13 out of 28 achieved stable disease (46.5%). The median survival time was 23.8 weeks. Neutropenia, grade 3 and 4 occurred in 38.8 per cent of all cycles. Skin rashes, diarrhea, asthenia, alopecia, neuropathy and edema were common non-hematologic toxicities.

Docetaxel should be considered as second line chemotherapy in advanced NSCLC when primary chemotherapy including cisplatin and/or paclitaxel had failed.

Key word : Non-Small Cell Lung Cancer, Docetaxel, Second-Line Chemotherapy

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Among chemotherapeutic agents with activity against non-small cell lung cancer (NSCLC), cisplatin has been considered the most important both in the palliative treatment of metastatic (stage IV) disease and combined-modality therapy of stage III disease. In stage IV NSCLC, cisplatin-based chemotherapy resulted in an improved survival time compared with supportive care alone[1,2]. In an analysis of over 2,000 patients with advanced NSCLC, who were treated on trials conducted by the Southwest Oncology Group, cisplatin emerged as an independent prognostic variable predicting on improved survival time[3]. Similarly, in stage III disease, combined-modality therapy with cisplatin chemotherapy, either in combination with radiotherapy or before surgery, was reported to improve the chance of survival compared with either radiotherapy or surgery alone[4,5]. Despite these contributions, de novo resistance to platinum compounds is common, and acquired resistance emerges rapidly during therapy. Thus, platinum resistance serves as both a preclinical and clinical model for drug development in NSCLC and a number of other neoplasms.

Several new chemotherapeutic agents have shown single agent activity in chemotherapy naive NSCLC, including taxanes, vinorelbine, gemcitabine, and irinotecan[6]. Recent phase III trials of new agent-platinum combinations have reported an improved response rate and a longer survival time compared with cisplatin alone or older cisplatin-based regimens [7,8]. Although second line chemotherapy may induce a response in platinum responding patients at the time of relapse, few if any of these promising new agents have demonstrated reproducible activity in patients with platinum-refractory NSCLC[9,10]. In view of the central role of platinum compounds in the primary therapy of stage III and IV patients, identification of new chemotherapeutic agents capable of inducing response in this setting of platinum-refractory disease is of increasing importance.

Of the new chemotherapeutic agents tested to date in platinum-treated NSCLC, docetaxel seems to be the most promising. In two previous single-institution phase II studies of docetaxel, as a second-line therapy in platinum-treated NSCLC, the aggregate response rate and median duration of survival were 17 per cent and 8.9 months, respectively[11-13]. Here, the authors report the results of docetaxel in a defined population of platinum-treated patients with NSCLC, most of whom had cisplatin or carboplatin-based regimens (platinum-refractory).

PATIENTS AND METHOD

Patient selection

Patients with histologically or cytologically confirmed unresectable or metastatic non-small cell lung cancer were eligible for the study. They were required to have a life expectancy of at least 12 weeks and a performance status of ≤ 2 (ECOG scale). Patients had to have a progression of their disease after the first treatment of chemotherapy.

Within 2 weeks of their registration into the study, each patient had their disease staged by a chest radiograph. Bone and CT scans of the chest and upper abdomen were carried out only in case the chest radiograph was not measurable. Within 3 days from the start of treatment and before each subsequent course of chemotherapy, patients underwent a history and physical examination, complete blood cell count, liver and renal function test and chest radiograph. During treatment, patient monitoring which included a weekly blood count, liver and renal function test and chest radiograph, were performed before each subsequent course of chemotherapy.

Treatment plan

The starting dose of docetaxel was 75 mg/m^2 administered in 250 ml of 5 per cent dextrose or 0.9 per cent saline as a 1-hour intravenous infusion. Therapy was repeated every 21 days provided the patients had sufficiently recovered from drug-related side effects. Treatment was continued until there was evidence of disease progression or unacceptable toxicity. Hematopoietic growth factors were not used prophylactically. Premedication of 50 mg of diphenhydramine intravenously, and dexamethasone at 10 mg intravenously were given to all patients 30 minutes before docetaxel. Patients who experienced a hypersensitive reaction during treatment received a second dose of diphenhydramine of 50 mg intravenously and dexamethasone of 10 mg intravenously, after which the docetaxel infusion was resumed. Dexamethasone of 16 mg/day orally was continued for 3 days.

Response and toxicity evaluation

Designations of complete response, partial response, no change and progressive disease were based on the standardized response definitions established by the World Health Organization. Duration of response was calculated from the time of the first documentation of disease progression. Toxicity evaluations were based on the National Cancer Institute common toxicity criteria.

Table 1. Patient characteristics.

	Cases	
Number (entered)	34	
Lost follow-up after 1 course	6	
Early death	3	
Previous Chemotherapy		
Paclitaxel/carboplatin	12	
Cisplatin/gemcitabine	8	
Cisplatin/vinblastine	7	
Cisplatin/etoposide	2	
Others	5	
Previous Radiation		
Primary tumor	7	
Whole brain RT	3	
Duration from Last Chemo.		
< 6 mos	20	
> 6-12 mos	9	
> 12-24 mos	3	
> 24 mos	2	
Histologic Diagnosis		
Adenocarcinoma	18	
Squamous cell CA	3	
Large cell CA	3	
Undiff NSCLC	4	
Response		
Partial response	3/28	10.7%
Stable disease	13/28	46.5%
Progression of disease	12/28	42.8%

RESULTS

Between January 1999 and June 2000, 34 patients were enrolled into this study. The characteristics of all 34 patients are listed in Table 1. The most common histologic type tumor was adenocarcinoma (61%) and a majority of patients had a Karnofsky performance status of 70 per cent.

Prior therapies received by these patients are listed in Table 1. Seven patients had received radiotherapy before and 2 had undergone surgery. All patients had received one or two regimens of chemotherapy. All were considered platinum-refractory. Twenty cases had progression of disease after stopping chemotherapy for less than 6 months.

Responses were evaluated in 28 patients. Responses from six patients were not assessable because they were lost to follow-up after the first cycle of treatment. Three cases died shortly after receiving the first course of chemotherapy.

Three of 28 assessable patients (10.7%) achieved a partial response, 13 had no change (after a minimum of two courses) and 12 had progressive disease. The median response duration was 20 weeks. The median survival time was 23.8 weeks.

Toxicity

A total of 162 cycles of docetaxel were administered. Toxicity was evaluated for all patients. Grade 3 and 4 leukopenia was found in 16.6 per cent (neutropenia 38.8% of cases). There were 5 episodes of febrile neutropenia. Thrombocytopenia grade 3 and 4 were found in 0.02 per cent.

The nonhematologic side effects of docetaxel were noted during all courses of treatment which were diarrhea, rash, asthenia, alopecia, phlebitis and mild neuropathy.

DISCUSSION

The presented response rate of 10.7 per cent in this platinum-refractory group of patients was lower than that reported for docetaxel in chemotherapy-naïve patients[13]. However, this was not unexpected, since failure to respond to first-line treatment may be a predictor of the failure of response to subsequent chemotherapy.

The projected median survival duration of 23.8 weeks in this study was striking. In fact, this was comparable to that seen in single agent chemotherapy in chemotherapy-naïve patients.

In conclusion, docetaxel, which has been shown by the authors and others to be active against chemotherapy-naïve non-small-cell lung cancer, retains a notable degree of activity against non-small-cell lung cancer that has been refractory to prior treatment with cisplatin.

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การรักษามะเร็งปอดด้วยยา Docetaxel

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การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิภาพและความปลอดภัยของยาเคมีบำบัด docetaxel ในการรักษามะเร็งปอดชนิด non-small cell ซึ่งเคยได้รับยาเคมีบำบัดมาก่อนแล้ว ผู้ป่วยจำนวน 34 ราย ได้รับการรักษาด้วยยา docetaxel ขนาด 75 มก/ม^2 โดยให้หยดเข้าหลอดเลือดนาน 1 ชั่วโมง ซ้ำยาทุก 3 สัปดาห์ โดยจะมีการให้ยาสเตียรอยด์ก่อนการรักษาด้วย docetaxel ทุกครั้ง จากผู้ป่วยจำนวน 28 ราย ที่ประเมินผลได้ ผู้ป่วย 18 รายเป็นมะเร็งชนิด adenocarcinoma, 3 ราย เป็น squamous cell และ 4 รายเป็น undifferentiated carcinoma ผู้ป่วยชาย 16 ราย หญิง 12 ราย อายุเฉลี่ยเท่ากับ 55 ปี (33-73 ปี) และค่าเฉลี่ยของ Karnofsky performance status เท่ากับ 70% (60-90%) ผู้ป่วยร้อยละ 19.2 มีโรคกระจายไปที่ตับ ร้อยละ 11.5 มีการกระจายโรคไปที่สมอง ร้อยละ 23 มีการกระจายโรคไปที่กระดูก และร้อยละ 65.3 มีการกระจายโรคในปอด ผู้ป่วย 17 ราย (ร้อยละ 50) เคยได้รับยา cisplatin มาก่อน ผู้ป่วย 12 ราย เคยได้รับยา paclitaxel ร่วมกับ carboplatin ก่อนที่จะมารับการรักษาด้วยยา docetaxel นอกจากยาเคมีบำบัดแล้วผู้ป่วย 7 รายเคยได้รับการฉายรังสีบริเวณรอยโรคที่ปอด และ 2 ราย เคยได้รับการฉายรังสีบริเวณรอยโรคที่สมอง ผู้ป่วยหนึ่งรายเคยได้รับการผ่าตัดก้อนในปอดและ 2 รายเคยได้รับการรักษาน้ำในช่องเยื่อหุ้มปอดชนิดร้าย malignant effusion (thoracoscopic surgery) ระยะช่วงเวลาหลังจากผู้ป่วยหยุดยาเคมีบำบัดชุดแรกมาถึงเริ่มการรักษาด้วยยา docetaxel พบว่าผู้ป่วย 20 ราย หยุดยามาน้อยกว่า 6 เดือน ผู้ป่วย 9 ราย หยุดยามา 6-12 เดือน ผู้ป่วย 3 ราย หยุดยามานาน 12-24 เดือน และผู้ป่วย 2 ราย หยุดยามานานเกิน 24 เดือน ผู้ป่วย 1 ราย เคยเป็นมะเร็งปอดชนิด small cell มาก่อนและต่อมาเกิดเป็น non-small cell ผลการรักษาพบว่าผู้ป่วย 3 ราย จาก 28 ราย (ร้อยละ 10.7) ตอบสนองต่อการรักษาแบบ partial response และผู้ป่วย 13 ราย จาก 28 ราย ตอบสนองต่อการรักษาแบบ stable disease (ร้อยละ 46.5) ค่าเฉลี่ยของระยะเวลารอดชีวิตของผู้ป่วยเท่ากับ 23.8 สัปดาห์ ผลข้างเคียงที่พบบ่อยคือภาวะเม็ดโลหิตขาวต่ำ (เกรด 3 และ 4) พบได้ร้อยละ 38.8 ผลข้างเคียงอื่นที่พบได้คือ การมีผื่นผิวหนัง, อาการท้องเดิน, อาการอ่อนเพลีย, ผมร่วง, อาการชาและอาการบวม

สรุป ยา docetaxel สามารถนำมาใช้เป็นยาเคมีบำบัดชุดที่สองในผู้ป่วยมะเร็งปอดชนิด non-small cell ซึ่งเคยได้รับยาบำบัดกลุ่ม cisplatin มาก่อน

คำสำคัญ : มะเร็งปอดชนิด non-small cell, ยาเคมีบำบัดชุดที่สอง, โดซีแท็กเซล

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