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Docetaxel: meeting the challenge of non-small cell lung cancer management

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The combined results of four phase II studies of docetaxel in non-small-cell lung cancer (NSCLC) are presented. All patients had either locally advanced (stage IIIb) or metastatic (stage IV) disease. Results are given for the 248 patients included in the trials who received docetaxel at a dose of 100 mg/m^2 given by intravenous infusion every 21 days on an outpatient basis. Among 200 patients evaluable for response, the overall response rate was 31.3% in 128 previously untreated patients and 19.4% in 72 previously treated patients. A subgroup of 30 previously treated patients who were platinum-refractory achieved a response rate of 13.5%. In previously untreated and previously treated patients, median duration of response was 24.6 weeks and 28.7 weeks, respectively, with median times to progression of 14.4 weeks and 13.6 weeks and median survival durations of 9.0 months and 8.1 months. Similar response rates were achieved in patients with stage IIIb and stage IV disease (32% and 25%, respectively) and in patients with visceral metastases (28%) although patients with single-organ involvement did better than those with two or more organs involved. Response rates were comparable to or better than those seen with previous single-agent chemotherapeutic regimens for advanced NSCLC and even with some combination treatments, with a tolerable adverse event profile.

Introduction

Lung cancer is the second most common malignancy and the leading cause of cancer death in North America and the UK.[1,2] In the United States, health statistics for 1993 revealed 170,000 new cases of lung cancer and 148,000 lung cancer-related deaths.[2] In England and Wales alone there were 34,000 deaths from this disease in 1991.[3] Worldwide, the projected number of cases is expected to exceed two million by the year 2000.[4] About 80% of lung cancers are defined as non-small cell lung cancer (NSCLC) on the basis of histologic examination.[3,5,6] These include squamous cell (epidermoid) cancer, large-cell cancer, and adenocarcinoma of the lung. For disease that is confined to the lung (stage I and II), surgery is the treatment of choice.[6] Unfortunately, about 65–75% of patients with NSCLC have locally advanced cancer or metastatic disease at presentation (stages III and IV).[3,6]

In contrast to results with small-cell lung cancer, chemotherapy has shown minimal benefit in patients with NSCLC.[6] Although the percentage cure rate nearly trebled between 1963 and 1993, from 5% to 13%, it remains one of the lowest cure rates among all malignancies.[2] More recently, response rates of over 15% have been achieved with single-agent chemotherapy, and 30–35% with platinum-containing combination therapy,[3,6] but the survival benefit compared to best supportive care has still been questioned.[7–12] The search for new, more effective agents or combination treatments therefore continues. Docetaxel is a new agent belonging to the taxoid group of chemotherapeutic drugs.[13–15] Results from phase I studies including patients with NSCLC suggested that docetaxel has some activity in this patient group.[16] A number of phase II studies have therefore been undertaken, in North America and Europe, to evaluate the efficacy of docetaxel in previously untreated, previously treated and platinum-refractory patients with advanced stage IIIb or IV NSCLC. The findings are presented below.

Patients and methods

Patient characteristics

Four phase II studies of docetaxel have been carried out at three centers in the US (the M.D. Anderson Cancer Center, Texas;[17] the University of Texas Health and Science Center, Texas; and the Memorial Sloan-

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Table 1. Patient characteristics: disease stage, histology and visceral involvement

Characteristic	Patients *n* (%)
Disease stage	
Locally advanced (Stage IIIb)	49 (18.3)
Metastatic (Stage IV)	219 (81.7)
Histology	
Adenocarcinoma	155 (57.8)
Squamous cell, large cell or unclassified	113 (42.2)
Additional visceral involvement	
At least one organ	256 (96)
Two or more organs	193 (72)

Table 2. Response (WHO criteria) to docetaxel 100 mg/m^2 in NSCLC

	Previously untreated	Previously treated [a]	Platinum-refractory [a]
Evaluable patients	128	72	30
Overall response rate, % (95% CI)	31.3 (23.2–39.3)	19.4 (11.1–30.5)	13.5 (4.5–30.7)
Median duration of response (weeks)	24.6	28.7	NA
Median time to progression (weeks)	14.4	13.6	12.0
Median survival (months)	9.0	8.1	7.4

[a] The 72 previously treated patients include the 30 platinum-refractory patients, whose results are also shown separately. NA: not applicable (too few responders).

Kettering Cancer Center, New York[18]) and in one European study group (the European Organization for Research on Treatment of Cancer (EORTC)–Early Clinical Trial Group (ECTG)). A total of 268 NSCLC patients were enrolled in the trials. They comprised 166 males and 102 females, with a median age of 61 years (range 29–79 years) and a median WHO performance status of 1 (range 0–2).

Forty-nine patients had locally advanced cancer but most had metastatic disease at entry (Table 1). Adenocarcinoma was the most commonly observed histology, while others included squamous cell carcinoma, large cell carcinoma and unclassified types. The great majority of patients had visceral involvement, with 72% having two or more organs involved (Table 1).

In order to be eligible for the trial, patients had to have a Karnofsky performance status of at least 60% or a Zubrod's performance status of no more than two, with adequate bone marrow, hepatic and renal function. In addition, patients with metastatic disease had either bidimensionally measurable or assessable indicator lesions on physical examination.

In total, 179 (67%) patients were chemotherapy-naïve and 89 (33%) had received previous platinum-containing treatment for advanced or metastatic NSCLC. Failure on platinum-containing therapy (cisplatin or carboplatin) was defined as progressive disease, no response for two cycles or more, or recurrence after adjuvant treatment.

Treatment

Docetaxel was administered at doses of either 100 mg/m^2 (248 patients) or 75 mg/m^2 (20 patients) and was given as an intravenous infusion over 1 h every 3 weeks on an outpatient basis. Patients received either no premedication or diphenhydramine 50 mg intravenously over 30 min prior to docetaxel infusion. Neither antiemetics nor growth factors were used prophylactically.

Evaluation of response

In each study, responses were defined as complete remission, partial remission, no change, or progressive disease, according to WHO criteria. Duration of response was determined as the interval between the first day of treatment and the first date on which disease progression was objectively documented. Time to progression was calculated as time from first docetaxel infusion to the first objective evidence of tumor progression.

Results

Results are presented for the 248 patients who received docetaxel at the dose of 100 mg/m^2. The median number of cycles administered to each patient was 4 (range 1–15), with a median ratio of dose given/intended dose (RDI) of 0.95 (range 0.14–1.16).

Response

Two hundred of the 248 patients were evaluable for response (i.e. met all eligibility and evaluability criteria called for by the study protocol). Overall response rates were better in the previously untreated patients than in the previously treated patients (31.3% vs

Table 3. Overall response rates according to disease stage and histologic type, and in patients with visceral metastases

	Overall response rate (%)
Disease stage	
Locally advanced (Stage IIIb)	32
Metastatic (Stage IV)	25
Histologic type	
Adenocarcinoma	31
Large cell	19
Squamous cell	16
Carcinoma (not specified)	29
Patients with visceral metastases	28

Table 4. Response according to number of organs involved

Number of organs	Previously untreated (%)	Previously treated [a] (%)	Platinum-refractory [a] (%)
1	43	29	30
2	26	11	0
≥ 3	28	19	10

[a] The 72 previously treated patients include the 30 platinum-refractory patients, whose results are also shown separately.

19.4%, respectively), but there was little difference between the groups in terms of duration of response, time to progression and survival duration (Table 2). The subgroup of platinum-refractory patients showed the lowest overall response rate, although survival duration was not significantly shorter than that seen in previously treated patients as a whole group.

Overall, there was no significant difference in the response rates achieved in patients with locally advanced disease or with metastatic disease (31.6% vs 24.9%, respectively; Table 3). Patients with adenocarcinoma and nonspecified carcinoma responded better than those with large cell or squamous cell carcinoma (29–31% vs 16–19%, respectively; Table 3). Interestingly, the response rate in patients with visceral metastases was high (27.7%, Table 3), with no statistically significant differences observed between the first- and second-line treatment groups. However, a large difference in response rate was observed between patients with only single-organ involvement compared to those with two or more organs involved, in both previously untreated and previously treated patients (Table 4). There was no significant difference between the median RDI in the 128 previously untreated patients (0.96, range 0.46–1.10) and that in the 72 previously treated patients (0.92, range 0.14–1.16).

Adverse events

Short-lasting neutropenia (grade 3–4) was experienced by the majority of patients (70%). However, neutropenic fever requiring antibiotic therapy occurred in only 4.5% of the treatment cycles. Almost all patients experienced some alopecia. In addition, about 40% developed fluid retention, manifested as peripheral edema and/or pleural effusion. Other adverse events included mucositis, diarrhea, skin reactions, peripheral neuropathy, asthenia, and onychodystrophy.

Discussion

The modest response rates to chemotherapy with single agents such as cisplatin, ifosfamide, mitomycin, vinblastine and vindesine in NSCLC patients [3] do not support their use as standard treatment for this disease. Even combination therapies appear to have questionable survival benefits.[8–12] However, a major study by the National Cancer Institute of Canada (NCIC) did show a survival advantage for combination therapy compared to best supportive care.[7] In this study, 251 patients with inoperable NSCLC received either VP (vindesine and cisplatin at a dose of 120 mg/m^2) or CAP (cyclophosphamide, doxorubicin and cisplatin 40 mg/m^2) or supportive care (including palliative radiotherapy and corticosteroid treatment).[7] Overall response rates were 15% on CAP and 25% on VP, with no response recorded for best supportive care. Median survival duration was significantly longer with either VP or CAP compared to best supportive care (33 weeks, 25 weeks and 17 weeks, respectively).

Elsewhere, response rates of 30–40% have been reported using modern chemotherapy regimens,[19–21] and a literature-based meta-analysis of published polychemotherapy trials has shown a reduction in mortality together with an improved quality of life in patients with nonresectable NSCLC.[22]

The cost of chemotherapy vs best supportive care has also been evaluated recently. A Canadian study concluded that the survival benefit achieved with polychemotherapy was associated with clear economic savings compared with that on best supportive care and that the majority of costs resulted from hospitalization and not from the use of chemotherapeutic agents.[22]

In this context, the results achieved with docetaxel in the trials described above indicate that this new

agent may have a role to play in the management of patients with locally advanced or metastatic NSCLC. The overall response rate was particularly good in the previously untreated patients (31.3%) but the response rate achieved in the previously treated patients (19.4%) was also good compared to previous results reported with single-agent chemotherapy.[3] Even in the subgroup of platinum-refractory patients, the response rate (13.5%) was better than that achieved with many other types of chemotherapy.[1] In terms of duration of response and time to progression, similar results were achieved in both patient groups, and there was a one-month difference in median survival duration (Table 2). Disease stage appeared to have little impact on response to docetaxel in these trials, with no significant difference in overall response rate (Table 3). The response rate also remained high (28%) in patients with visceral metastases, although there was a clear advantage to those with only single-organ involvement compared to those with two or more organs involved (Table 4). Histologic type was also shown to influence response to docetaxel, with the best results seen in patients with adenocarcinoma or nonspecified carcinoma compared to those with either large cell or squamous cell carcinoma (Table 3).

The median dose of docetaxel given was close to the intended dose of 100 mg/m^2 in both previously untreated and previously treated patients, suggesting that toxicity is tolerable in the majority of cases. Manifestations of fluid retention occurred in around 40% of patients but the onset of this effect can be delayed and its severity reduced by prophylactic administration of dexamethasone.

Conclusions

Docetaxel at a dose of 100 mg/m^2 given intravenously over 1 h every 21 days displayed significant activity in untreated, previously treated and even platinum-refractory patients with advanced (stage IIIb or IV) NSCLC. This activity was comparable to or better than that achieved with previous single-agent chemotherapeutic regimens and even some combination treatments, and was accompanied by a manageable adverse event profile. Additional studies investigating docetaxel both as a single agent and in combination with other active agents are in progress.

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