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New options in the treatment of non-small cell lung cancer

Frank Fossella,[1] James R Rigas[2] and Chandra P Belani[3]

[1]MD Anderson Cancer Center, Houston, Texas, USA. [2]Dartmouth Hitchcock Medical Center, Dartmouth, New Hampshire, USA. [3]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

The options for treating non-small cell lung cancer (NSCLC) were expanded by the introduction of the taxanes. As a single agent, docetaxel produced response rates ranging from 15 to 22% in evaluable patients in the second-line setting, with median duration of responses ranging from 5.6 to 7.5 months. To confirm the results observed in the phase II studies, a phase III trial was conducted. Three-hundred and seventy-three patients with advanced NSCLC who had failed prior platinum-based chemotherapy were randomized to receive docetaxel 100 mg/m², docetaxel 75 mg/m² or a reference arm consisting of vinorelbine or ifosfamide. Efficacy, safety and quality of life (using the Lung Cancer Symptom Scale) were assessed. Data from this study are forthcoming and may confirm the benefits provided by the inclusion of docetaxel in the second-line treatment of NSCLC. Docetaxel is also an active single agent in the first-line setting, with response rates ranging from 24 to 38% in evaluable patients, with a median survival of 6–13 months. Based on the single-agent activity, it was logical to evaluate the efficacy of docetaxel in combination with other active agents. As such, docetaxel has been studied in with numerous other agents such as vinorelbine, gemcitabine, platinums, etc. Notably cisplatin and carboplatin has shown promising rates of response and response duration in phase II trials. These combinations have now entered randomized phase III study. [© 1999 Lippincott Williams & Wilkins.]

Key words: Combination, docetaxel, first-line, non-small cell lung cancer, second-line.

Introduction

Among the important questions recently addressed by those involved in caring for patients with non-small cell lung cancer (NSCLC) are (i) whether chemotherapy has any benefit at all in this disease and (ii) whether there is a role for salvage treatment in the second-line setting.

Over the past 5 years, the meta-analysis of trial data has demonstrated that there is a modest but significant survival advantage when patients receiving cisplatin-based chemotherapy are compared with those given best supportive care alone.[1] The median survival in chemotherapy-treated patients is around 3 months longer and 1-year survival rates are increased from 10–15% to approximately 25%. However, any such survival advantage must be considered in the broader context of cancer-related symptoms, safety and overall quality of life (QoL). The recent trial by Cullen *et al.* suggests at least a trend towards improved life-quality in the recipients of cisplatin-based chemotherapy.[2]

In the many NSCLC patients with recurrent or refractory disease, few treatment options have been available. Response rates with chemotherapy have generally not exceeded 10% and there had until recently been no phase III trials in this setting.[3]

Docetaxel is one of the few drugs which has been systematically evaluated in patients with platinum-refractory NSCLC. At least four phase II trials have studied 100 mg/m² docetaxel every 3 weeks in the second-line setting.[4–7] Taking the four trials together, almost 200 patients were treated. The response rates ranged from 15 to 22% and the median durations of response ranged from 5.6 to 7.5 months. In these studies, the estimated 1-year survival rates were 40 and 25%.[4–6]

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Correspondence to Dr F Fossella, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas, TX 77030-4009, USA.
Tel: (+1) 713 792-6363; Fax: (+1) 713 796-8655;
E-mail: ffossell@mdanderson.org

Given these indications of potentially meaningful response and survival benefit, a multicenter phase III study was designed to compare docetaxel with an alternative form of chemotherapy.[8]

Docetaxel versus vinorelbine or ifosfamide following failure of platinum-based chemotherapy

In this randomized phase III study, patients with advanced NSCLC who had progressed on or relapsed after at least one prior platinum-based regimen were randomized to receive docetaxel 100 mg/m^2 every 3 weeks, docetaxel 75 mg/m^2 every 3 weeks or a control regimen of vinorelbine 30 mg/m^2 on days 1, 8 and 15 or ifosfamide 2 g/m^2 (with standard dose mesna) on days 1–3 of every 3-week cycle.[8] (The control regimen was chosen at the individual investigator's discretion; the majority of patients received vinorelbine.)

Patient characteristics

Patients were stratified before randomization according to their best response to prior platinum (i.e. progressive disease or non-progressive disease) and their performance status (0 or 1 versus 2). Patients with prior exposure to paclitaxel were eligible for the study.

The median age was 59–60 years in all three groups. Across all treatment groups, two-thirds of those patients enrolled were male, the predominant histology was adenocarcinoma, 26–35% had received two or more prior chemotherapies and 30–40% had received prior paclitaxel.

QoL

As an integral part of the trial, patients' QoL and cancer-related symptoms were carefully assessed using the Lung Cancer Symptom Scale (LCSS), an instrument which has been validated in large studies in lung cancer populations.[9] The LCSS contains two elements. Firstly, a total of nine visual analog scales completed by the patient are used to measure the severity of six specific symptoms (appetite, fatigue, cough, dyspnea, hemoptysis and pain) and to assess three global aspects of QoL (normal activity, cancer symptoms and QoL today). Secondly, a five-point ordinal scale is completed by the observer (doctor or nurse) in relation to the six specific symptoms listed above. The LCSS was completed at baseline, immediately prior to each cycle of treatment, at the end of the study treatment and at every 2 months' follow-up thereafter.

In terms of patient characteristics, it worth noting that one-third of all the patients had disease in three or more organs, around 17% were of ECOG performance status 2 and around 40% had previously been treated with paclitaxel.

Patients were excluded from the QoL analysis if there was no assessment at baseline or during treatment, or if more than three patient observations or more than two observer ratings were missing at baseline or on-treatment. Overall, fewer than 30% of patients were excluded from the analysis. Importantly, the reasons for exclusion were evenly spread across the three arms of the study.

The data were subjected to several forms of analysis. The results presented here derive from an analysis of covariance. However, they are supported by the conclusions derived from longitudinal and pattern mixture modeling. The analysis of covariance was conducted on the intent-to-treat population, using paired QoL assessments (baseline to last available assessment, baseline to best score, baseline to cycle 2 and baseline to cycle 3). The model included as covariates age, sex, stage, weight loss, performance status, prior chemotherapy and radiotherapy, and prior platinum dose and response.

The results from this study are forthcoming and will be important in defining the role of docetaxel in the second-line treatment of NSCLC, and indeed the benefits of chemotherapy in this disease.

Docetaxel and cisplatin combinations

It is now established that chemotherapy in the first-line setting can extend the survival of patients with NSCLC, and that both first- and second-line chemotherapy can have a favorable impact on cancer-related symptoms.[3] However, the proportion of patients surviving for 1 year is small, and the aim of introducing new agents must be to increase this number and further to extend life expectancy. In this process all options must be considered. However, among the more promising of them is the combination of docetaxel with cisplatin, since both agents have consistently been shown to have activity in this disease.

Following initial pilot and phase I studies,[10–12] the doses chosen for our phase II trial were docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, both administered as a 1 h i.v. infusion every 21 days.[13]

Table 1. Patient characteristics of a phase II study of docetaxel in combination with cisplatin[13]

	No. of patients
Male/female	27/20
Median age [years (range)]	62 (45–78)
Performance status	
0	9 (19%)
1	38 (81%)
Stage:	
IIIB	3 (6%)
IV	44 (94%)
Median sites (range)	2 (1–4)
Histology	
Adenocarcinoma	26 (55%)
Large cell carcinoma	9 (19%)
Squamous cell carcinoma	6 (13%)
Other	6 (13%)

Dexamethasone was given 8 mg p.o. b.i.d. for 5 days starting on day −1. Treatment was continued until toxicity or progression. The primary variable was response rate, with response duration, time to disease progression, duration of survival and QoL as secondary endpoints.

Patient characteristics

The 47 patients treated had a median age of 62 years and a median number of two sites of disease (range 1–4). Eighty-one percent of patients were ECOG performance satus 1, 94% of patients had stage IV disease and adenocarcinoma was the dominant histology (55%) (Table 1).

The study in this context

The results from this phase II are forthcoming; however, there have been three other trials of the docetaxel/cisplatin combination in advanced NSCLC (Table 2).[14–18] In the Australian trial,[14,15] similar doses of each agent were used, the overall response rate (ORR) was 39% and the median survival 10 months. Le Chevalier *et al.*[16] used a higher dose of cisplatin (100 mg/m^2), and reported an ORR of 33% and median 8 month survival; and Androulakis used a higher dose of both docetaxel (100 mg/m^2) and cisplatin (80 mg/m^2), achieving an ORR of 48% and 13 month median survival.[17,18]

Subsequent to these studies, the ECOG is undertaking a randomized trial with patients assigned to one of four arms: the ECOG reference arm of paclitaxel 135 mg/m^2 over 24 h plus cisplatin 75 mg/m^2 every 3 weeks; paclitaxel 225 mg/m^2 over 3 h plus carboplatin to achieve an AUC of 6 mg/min per ml every 3 weeks; gemcitabine 1000 mg/m^2 on days 1, 8 and 15 plus cisplatin 100 mg/m^2 every 4 weeks; or the regimen described above of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2.

The Hellenic group is also conducting a randomized trial comparing in this instance a non-platinum regimen of gemcitabine 1100 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 1 every 3 weeks with a regimen of docetaxel 100 mg/m^2 plus cisplatin 80 mg/m^2 every 3 weeks. As in their phase II study, primary prophylactic granulocyte colony stimulating factor will be administered.

Docetaxel plus carboplatin

Carboplatin may in certain respects be easier to combine with docetaxel. Following a phase I study,[19] the recommended dose of 80 mg/m^2 docetaxel plus carboplatin administered to obtain an AUC of 6 mg/ml per min was taken into a phase II study.[20,21] Dexamethasone was given at a dose of 8 mg p.o. b.i.d. for 3 days. Treatment continued until toxicity or progression.

Table 2. Overview of phase II studies with docetaxel in combination with cisplatin[13–18]

	Belani[13]	Zalcberg[14,15]	Le Chevalier[16]	Androulakis[17,18]
No. of patients	47	47	51	53
Schema				
Docetaxel (mg/m^2)	75	75	75	100
Cisplatin (mg/m^2)	75	75	100	80
Granulocyte colony stimulating factor	–	–	–	+
Efficacy				
Overall response rate (%)	32	39	33	48
Time to progression (months)	–	4	4	5
Median survival (months)	11.5	10	8	13

Data are available for the first part of this phase II trial were encouraging. Given this promising evidence of activity with this combination, a multicenter phase III study has been designed in which patients are randomized to docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks, docetaxel 75 mg/m^2 plus carboplatin to an AUC of 6 every 3 weeks or vinorelbine 25 mg/m^2 weekly plus cisplatin 100 mg/m^2 on day 1 every 4 weeks.

Discussion

The phase III comparison of docetaxel versus vinorelbine or ifosfamide may represent the first conducted prospective, randomized phase III trial to validate the benefits associated with a second-line treatment in NSCLC.

In an effort further to improve the prospects for patients with advanced NSCLC, several combination regimens have already been successfully piloted and are now in phase III trial. These include the combination of docetaxel with either cisplatin or carboplatin. In the future, it is likely that other novel agents with activity in this disease, such as vinorelbine, gemcitabine, irinotecan and new taxanes, will find a place in trials of combination therapy. There are already promising early results with the combination of docetaxel with vinorelbine and with gemcitabine. Further ahead is the possibility of using highly active combination regimens in the adjuvant and neoadjuvant settings.

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