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Short paper

A phase II trial of docetaxel in advanced non-small cell lung cancer

A Saarinen,[1] A Jekunen,[2] M Halme, S Pyrhönen,[2] K Tamminen,[1] R Boyer,[3] N Roubille[3] and K Mattson[1]

Departments of [1]Internal Medicine and [2]Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland. Tel: (+358) 4712270; Fax: (+358) 2418717. [3]Rhone-Poulenc Rorer, Antony, France.

Twenty-nine patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) were treated with docetaxel. Ten patients had already received chemotherapy, the others had received no chemotherapy. Docetaxel was administrated i.v. over 60 min every 21 days at a dose of 100 mg/m^2. Twenty-three patients were evaluable for response. There were no complete responses and eight partial responses. The overall response rate was 35% (28% in the intent to treat analysis). Median duration of response was 43 weeks and median time to progression 12 weeks. Neutropenic infections, neurotoxicity and asthenia were dose-limiting toxicities (6% of 118 cycles). The other main toxicities were asthenia in 48%, skin reactions in 31% and nail changes in 31% of the patients. Single-agent docetaxel appears to be active against both previously treated and untreated advanced NSCLC. Toxicity was acceptable but should be carefully monitored.

Key words: Advanced non-small cell lung cancer, docetaxel, phase II trial, single agent.

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common causes of cancer death in men and women.[1] The majority of cases are diagnosed at an advanced stage, with corresponding poor prognoses, so there is an urgent need for novel and effective systemic therapy.

Docetaxel (Taxotere®) is a new taxoid, a semi-synthetic compound extracted from the needles of the European yew tree. It has been shown to be at least as active as its analog paclitaxel, achieving response rates of up to 38% when used as a single agent against previously untreated NSCLC.[2] Docetaxel has demonstrated activity against refractory solid tumors, which is encouraging for their use against NSCLC.

Correspondence to K Mattson

The primary objective of this study was to evaluate the response rate and toxicities of single-agent docetaxel. Time to progression and duration of response were also calculated.

Materials and methods

Patient selection

Thirty patients from Helsinki with locally advanced or metastatic NSCLC were enrolled in this multicenter phase II study. One patient died before initiation of the treatment and 29 received the treatment. Patient characteristics are given in Table 1. Nineteen patients (66%) had received no prior chemotherapy; 10 had been treated with gemcitabine or platinum compounds. Four patients (14%) had liver metastases and seven (24%) had bone metastases.

Treatment plan

Docetaxel was administered as an i.v. infusion over 60 min at a dose of 100 mg/m^2 every 21 days. Oral dexamethasone was given prophylactically, starting 13 h before docetaxel infusion and continuing for 96 h after the infusion (8 mg b.i.d.). The treatment was continued for six cycles. It was permitted to administer a further three cycles to those patients who achieved a response.

Response evaluation

Patients were evaluated for response at least after every three cycles and at the discontinuation of

Table 1. Patient characteristics

N (treated)	29
males	18
females	11
Age (years)	
38 45	1
46 60	12
61 78	16
Karnofsky index (%)	
100	3
80 90	14
60 70	12
Histology	
adeno	19
squamous	6
bronchoalveolar	2
large	2
Previously untreated	19
Previously treated	10
gemcitabine	7
platinum-based combination	3
Stage	
IV	19
other	10

treatment if they had not been evaluated within 28 days. Toxicity was assessed according to NCI criteria when applicable. Follow-up assessments were performed at least every 3 months. All the responses and no changes were assessed by a panel with two independent radiologists.

Results

On average patients received four cycles of docetaxel (range: one to eight). Twenty-three patients were evaluable for response. Reduced doses were admintrated in nine of 118 cycles (8%). The reasons for dose reduction were infections in three patients, neuropathy in three patients with asthenia in one patient.

No complete responses were observed, but eight patients achieved a partial response and seven patients had stable disease. The overall response rate was therefore 35% (28% in the intent to treat analysis). The responses were documented after two or three cycles in each case. The overall response rate in previously untreated patients was 41% (37% in the intent to treat analysis) and 17% in previously treated patients (10% in the intent to treat analysis). Median duration of response was 43 weeks and median time to progression was 12 weeks in the intent to treat analysis. Median survival was 41 weeks.

The major toxicity of this regimen was neutropenia. Grade 4 neutropenia developed in 43% of cycles and grade 3 in 7% of cycles. Neutropenia was invariably detected in the laboratory examination made on day 7 after infusion and never lasted more than 7 days. During 118 cycles, there occured three cases of febrile neutropenia with no infection focus and 16 cases of infections (12 with a verified locus and four with no known focus) treated with i.v. antibiotics. Three patients died of infections. No grade 3–4 thrombocytopenia occurred in this study.

Three patients (10%) experienced grade 3 neurosensory toxicity and two patients (7%) experienced grade 3 neuromotor and neurosensory toxicity. Grade 1–2 peripheral neuropathy occured in 14 patients (48%). Other frequently occuring non-hematological side effects were asthenia in 48% of patients, grade 1–2 skin reactions in 31%, nail changes in 31% and mild to moderate fluid retention in 24%. One moderate and one mild allergic reaction occurred during 118 infusions. Grade 3–4 nausea occurred in five patients with grade 3–4 vomiting in one patient and peptic ulcer in one patient.

Discussion

We achieved an overall response rate of 37% in the intent to treat analysis in chemotherapy-naive patients. In a meta-analysis based on four studies involving 160 previously untreated patients the response rate was 27%.[3] The small number of patients in our study may explain the difference in results.

However, we did not achieve the same level of response in previously treated patients as in two other studies of NSCLC patients who had failed prior platinum-containing chemotherapy. The meta-analysis of these studies shows a response rate of 17%.[3] Only three of our patients had received platinum-based therapy. Seven patients were refractory to gemcitabine. It may be that gemcitabine-resistant tumors are not suspectible to docetaxel, but our patient sample was too small for firm conclusions to be drawn.

In the previous studies of single-agent docetaxel neutropenia was the main dose-limiting event.[1] Our patients experienced frequent, but rapidly reversible, grade 4 neutropenia. As in the other studies,[1] thrombocytopenia was mild.

The incidence of neuropathy (58%) was the same as in the other reports.[3–5] However, we observed more cases of grade 3 neurotoxicity than in other studies.[5] Some patients with grade 2 neuropathy did

not receive reduced doses of docetaxel although this was permitted in the protocol, which may account for the increased incidence of grade 3 neuropathy. It is obvious that neurological status should be monitored carefully in patients being treated with docetaxel and dose reduction or discontinuation of treatment should be considered when grade 2 neuropathy occurs.

Two of our patients suffered from mild to moderate hypersensitivity reactions. No severe fluid retention was reported. Dexamethasone pre-medication seems to offer effective protection. The numbers of the other non-hematological events were similar to those reported by other investigators.[5]

Conclusion

We conclude that docetaxel is an effective agent against NSCLC and should be tested with other agents which are also active against NSCLC. Promising response rates (up to 53%) have been achieved using the docetaxel cisplatin combination.[6,7] Other combinations and schedules using docetaxel with other agents should also be studied.

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