Pergamon

European Journal of Cancer Vol. 31A, Suppl. 4, pp. S18–S20, 1995

0959–8049/95 $9.50+0.00

0959-8049(95)00358-4

Docetaxel in Stage III and IV Non-small Cell Lung Cancer

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Phase II studies have been conducted to evaluate the efficacy and tolerability of docetaxel in the treatment of patients with advanced non-small cell lung cancer (NSCLC). Docetaxel was administered to patients with stage III and IV NSCLC at a dose of 100 mg/m^2 intravenously over 1 h every 3 weeks. Patients included in these four phase II studies had received either no prior chemotherapy (n = 114) or treatment with cisplatin- or carboplatin-containing regimens (n = 57). Major objective response rates were reported in 33–38% of previously untreated evaluable patients and in 21–27% of previously treated evaluable patients. Neutropenia was the most common adverse event. Non-haematological adverse events included hypersensitivity reactions, skin rash, alopecia and fluid retention. Docetaxel demonstrates significant antitumour activity in patients with advanced NSCLC. Further investigations of this agent with corticosteroid premedication, colony-stimulating factors and other agents active in NSCLC are indicated.

Key words: docetaxel, phase II clinical studies, non-small cell lung cancer
Eur J Cancer, Vol. 31A, Suppl. 4, pp. S18–S20, 1995

INTRODUCTION

LUNG CANCER is the most common cancer in the world, with approximately 900 000 new cases occurring each year [1]. In the U.S.A., an estimated 172 000 new cases of lung cancer will occur in 1994 [2]. This will result in 153 000 cancer deaths and make lung cancer the leading cause of cancer-related mortality. Most of these lung cancer deaths will be attributed to metastatic non-small cell lung cancer (NSCLC). Currently, the major advances in the treatment of this disease are in the development of systemic therapies that have been most successful when used in combination with surgery or radiotherapy for the treatment of locally advanced (stage III) NSCLC. The key to continued progress will be the identification of new active chemotherapeutic agents in phase II clinical trials. Since 1976, over 20 such agents have been studied in phase II studies in NSCLC patients at Memorial Sloan-Kettering Cancer Center (MSKCC), U.S.A. Of these, four have demonstrated significant antitumour activity (>15% response rate) in NSCLC: cisplatin, vindesine, edatrexate and docetaxel.

Docetaxel (Taxotere®) is a semisynthetic taxoid prepared from a non-cytotoxic precursor, 10-deacetylbaccatin III, extracted from the needles of the European yew, *Taxus baccata* L. [3–5]. This unique cancer chemotherapeutic agent works by promoting tubulin assembly into microtubules, stabilising microtubules and inhibiting depolymerisation to free tubulin, thus blocking cells in the M phase of the cell cycle [6, 7]. In preclinical studies, docetaxel was moderately active against Lewis lung carcinoma, without significant schedule dependency for activity [8]. Phase I trials were conducted at five institutions in the U.S.A. and Europe using various administration schedules [9–13]. The recommended dose of docetaxel for phase II studies was 100 mg/m^2 as a 1 h intravenous (i.v.) infusion every 3 weeks. The dose-limiting adverse event was neutropenia, and two partial responses were reported in patients with NSCLC.

This paper will discuss the results of the MSKCC phase II trial [14] and three similarly designed studies conducted in the U.S.A. and Europe with docetaxel in patients with NSCLC [15–18]. The last three studies have been published in abstract form only and many details are unavailable.

PATIENTS AND METHODS

Patients

The one European [15] and three U.S.A. cancer centres [14, 16–18] discussed in this review enrolled a total of 171 patients with clinically unresectable stage III or IV NSCLC (including 57 patients who had previously received cisplatin- or carboplatin-containing chemotherapy) into similarly designed phase II studies.

Treatment

In all studies, patients received docetaxel at a dose of 100 mg/m^2 i.v. over 1 h, every 3 weeks. According to the MSKCC protocol, patients who experienced a major objective response or no change continued to receive docetaxel until there was either evidence of disease progression or unacceptable adverse events occurred. Dosage reductions in subsequent cycles to 75 mg/m^2 were allowed in the event of febrile grade III or IV neutropenia requiring parenteral antibiotics. Prophylactic colony-stimulating factors were not given. A dose reduction was also planned for grade III adverse events (other than infusion-related hypersensitivity reactions) and grade II peripheral neuropathy. A maximum of two 25% dose reductions were allowed per patient. If a patient developed grade III adverse events, the subsequent dose was delayed until the adverse event resolved.

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Assessment of efficacy

In the MSKCC study, assessment of antitumour response was made every 3 weeks by physical examination and chest X-ray, and every 6 weeks by CT scan. Major therapeutic responses were defined as either complete remission (CR) or partial remission (PR) for patients with measurable indicator lesions, and CR or improvement (a major response category) for those with evaluable indicator lesions. Major responses were confirmed by repeat tumour assessment after a minimum of 4 weeks. 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. All major responses were reviewed by a reference radiologist and an external review panel.

RESULTS

The median age of patients included in these phase II studies was approximately 60 years (range 55–60). Where data are given, more than 75% of the patients in each of the studies had a diagnosis of adenocarcinoma or squamous cell carcinoma. Patients who had not received previous chemotherapy may have had prior surgery or radiotherapy. Patients who were "platinum-refractory" had had either progressive disease whilst receiving platinum-containing chemotherapy or no response to ⩾2 cycles of platinum-containing chemotherapy.

The antitumour response rates achieved by the MSKCC, U.S.A. [14], the Early Clinical Trials Group of the European Organization for Research and Treatment of Cancer [15], the University of Texas MD Anderson Cancer Center, U.S.A. [16], 17], and the University of Texas Health Science Center at San Antonio, U.S.A. [18] are shown in Table 1. The overall major objective response rate was 34% (range 33–38%) for patients who had received no prior chemotherapy and 24% (range 21–27%) for patients who had previously received cisplatin- or carboplatin-containing chemotherapeutic regimens.

Grade IV neutropenia was the most common adverse event in all trials. This was generally of brief duration and well tolerated. Other adverse events reported during these studies included infusion-associated hypersensitivity reactions (easily treated by interrupting the infusion), dermatitis, and alopecia. Fluid retention (with peripheral oedema and/or pleural effusion) was an unexpected finding; this occurred later in treatment and was related to the cumulative dose of docetaxel received.

Table 1. Antitumour response rates for docetaxel in stages III and IV non-small cell lung cancer

		First line		Second line*	
Reference	Treatment centre	No. of evaluable patients	Response rate (%)	No. of evaluable patients	Response rate (%)
[16, 17]	MDACC	39	33%	42	21%
[15]	EORTC	32†	33%	–	–
[18]	SA	14†	33%	15†	27%
[14]	MSKCC	29	38%	–	–
	Total	114	34%	57	24%

MDACC, MD Anderson Cancer Center, U.S.A.; EORTC, European Organization for Research and Treatment of Cancer; SA, The University of Texas Health Science Center at San Antonio, U.S.A.; MSKCC, Memorial Sloan-Kettering Cancer Center, U.S.A.

*Patients had previously been treated with cisplatin- or carboplatin-containing regimens; †Disease assessment was considered too early in several patients in each of these studies.

DISCUSSION

Antitumour response rates of 18–22% have been observed with cisplatin, ifosfamide, mitomycin, and the vinca alkaloids (vinblastine and vindesine) as initial therapy in patients with inoperable NSCLC [19, 20]. These agents administered in combination produce response rates of 30–51% in patients with advanced disease [21], and have improved survival of patients with resectable stage IIIA disease when given pre-operatively [22, 23].

The major objective antitumour response rate of 38% for docetaxel is the highest rate observed for any single agent tested in NSCLC patients at MSKCC, U.S.A. If this high response rate can be confirmed in randomised studies, docetaxel may represent an important advance in the treatment of NSCLC. Importantly, docetaxel produced an objective response in nearly 25% of patients with NSCLC refractory to platinum-containing regimens. This apparent lack of cross-resistance with platinum is an interesting finding and may offer some hope for this group of patients with a poor prognosis.

In view of the high level of activity of docetaxel in this setting, development of combination chemotherapy regimens with other agents of known activity in NSCLC is warranted. Future studies should consider the use of colony-stimulating factors, prophylactic antibiotics, and corticosteroid premedication to diminish docetaxel-related adverse effects (febrile neutropenia, rash and fluid retention). Moreover, future studies must consider including components to evaluate the impact of docetaxel therapy on patient quality of life.

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Acknowledgement—This study was supported in part by a research grant from Rhône-Poulenc Rorer.