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European Journal of Cancer 40 (2004) 2071–2076

European Journal of Cancer

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Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer

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Received 12 May 2004; accepted 12 May 2004
Available online 27 July 2004

Abstract

We report the results of a randomised phase II trial of docetaxel tested as a single agent in patients with recurrent head and neck cancer using methotrexate as a control arm to validate the results. Eligibility criteria included: histologically-confirmed squamous cell carcinoma, measurable disease, adequate haematological, renal and hepatic functions, no prior chemotherapy for recurrent cancer, signed informed consent. 40 mg/m^2 methotrexate was given as a short weekly bolus in injection, and 40 mg/m^2 docetaxel was administered as a one hour weekly infusion. A total of 57 patients were randomised based on a ratio of 2/1:37 and 20 patients received docetaxel and methotrexate, respectively. Patient characteristics included 49 males and 8 females; the median age was 59 years (range: 43–82 years). Twenty-eight patients had a local-regional relapse and 29 had distant metastasis, the median disease-free interval was 7.9 months (range: 0–165 months). For patients treated with docetaxel, the following grade 3–4 toxicities occurred: neutropenia (12.5%) with febrile neutropenia in one patient (1%), anaemia (19%) mucositis (9%) and ungueal toxicity (9%). In the methotrexate arm, the grade 3–4 toxicities were: anaemia (15%) and mucositis (5%). The response rate was significantly higher in the docetaxel arm with 27% (95% confidence interval (CI): 21.7–32.3%) of objective responses versus 15% (95% CI: 11.2–18.8%) in the methotrexate arm. Overall survival and time to progression were super-imposable between the docetaxel and methotrexate treatments. Docetaxel given as a weekly infusion has a high activity in patients with head and neck cancer. A phase III trial is needed to test if this translates into a survival benefit for docetaxel use.

Keywords: Methotrexate; Docetaxel; Taxotere™; Randomised trial; Head and neck squamous cell carcinoma; Recurrence

1. Introduction

Squamous cell carcinoma of the head and neck is the sixth most common form of cancer, worldwide. In the European Union (EU), more than 70 000 new cases of squamous cell carcinoma of the head and neck were diagnosed in 1998. Patients with early cancers of the head and neck region can be treated with surgery and radiation, with a high expectation of cure [1]. Unfortunately, at presentation, up to 75% of patients with head and neck cancer have advanced locoregional disease (T2-T4, N2-N3, M0). Despite aggressive treatment of the primary tumour, local-regional and/or a metastatic recurrence occurs in approximately 60% and 20% of

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doi:10.1016/j.ejca.2004.05.019

such patients, respectively. Both situations are considered as incurable and chemotherapy is commonly accepted as the standard palliative therapy. The objective of this therapy is to improve quality of life by reducing symptoms and extending patient survival. The prognosis in this patient population at the time of recurrent disease remains dismal with a median survival time of approximately six months [2]. Despite the better response rate obtained with combination chemotherapy, no survival advantage has been demonstrated over methotrexate as single agent treatment [3–5]. Thus, methotrexate monotherapy is still considered to be the standard chemotherapy in this situation by most medical oncologists. However, further investigations of new agents are needed to improve survival in this patient population. Docetaxel monotherapy has already shown high activity in patients with advanced or recurrent head and neck cancer. The reported response rates ranged from 20.8% to 42% with a three week 100 mg/m^2 schedule in three phase II trials [6–8]. Docetaxel given as a weekly infusion has been studied in several phase I trials [9]. The main proposed advantage of this schedule is to combine improved dose-intensity with reduced toxicity, in particular haematological toxicity. Relying on the high activity of docetaxel in patients with recurrent head and neck cancer and the feasibility of a weekly administration, we report the results of a randomised phase II trial with weekly docetaxel tested as a single agent using methotrexate as a control arm to validate the results.

2. Materials and methods

This study was an open-label, multi-centric, randomised trial of docetaxel versus methotrexate given as first-line chemotherapy for patients with local-regional or metastatic recurrent squamous cell carcinoma of the head and neck. The main inclusion criteria were: no prior chemotherapy, measurable disease, patient over 18 years of age, normal blood cell count, normal renal and hepatic function, performance status $\leqslant 2$ and signed informed consent. Initial exposure to chemotherapy during treatment of the primary tumour was allowed. The main exclusion criteria included: adenocarcinoma or undifferentiated carcinoma of the nasopharynx, known brain metastases and uncontrolled infection.

Patients were randomly assigned to the treatment arms in a ratio of 2/1 to receive docetaxel or methotrexate, respectively. The randomisation was stratified according to the duration of the disease-free interval ($>$ or $<$9 months) and the type of recurrence (local-regional or metastatic recurrence). Comparison of the objective response rate (ORR), between patients treated with docetaxel or methotrexate was the primary end-point of the study. Other objectives were to estimate the overall survival, the response duration, the time to progression and the toxicities.

Docetaxel was planned to be administered at a dose of 40 mg/m^2 as a weekly one hour infusion. 40 mg/m^2 methotrexate was administered weekly as a bolus intravenous injection (i.v.). Patients continued to receive treatment as assigned at randomisation until disease progression or the occurrence of excessive toxicity. The extent of the disease was evaluated by cervical computerised tomography (CT) scan, thoracic and liver CT scan within the three weeks preceding the start of the treatment. The activity was assessed according to the World Health Organisation (WHO) criteria. The activity assessment was repeated at six week intervals by physical examination and the same initial radiological procedure. Toxicities were assessed weekly according to the National Cancer Institute of Canada – Common Toxicity Criteria (NCIC – CTC) or the International Union Against Cancer (UICC) criteria.

3. Statistical analysis

The planned analyses were intended to evaluate docetaxel activity, and to validate the results using the methotrexate group. The main criterion was the ORR. Secondary criteria were overall survival, the response duration and the time to progression. The number of patients was calculated according to the method of Simon [10]. The study was designed to reject docetaxel if it was inactive i.e. with an ORR $< 8\%$. In case of outstanding activity i.e. with an ORR $> 40\%$, closure of the study was planned. In the investigational arm (docetaxel arm), the α and β risks were chosen at 5%. Then, 38 patients had to enter the docetaxel arm. In the methotrexate control arm, the α and β risks were chosen at 5% and 20%, respectively, because methotrexate activity is clearly established. Accepting α and β errors at 5% and 20%, 19 patients had to enter the methotrexate arm. According to a randomisation ratio of 2/1, a total of 57 patients had to enter the trial (Fig. 1). In case of insufficient activity i.e. if less than two patients had a response among the first 18 patients included in the docetaxel arm, the study could be stopped early. If more than 8 patients had a response in the docetaxel arm, docetaxel could be considered as a potentially active drug, the trial could thus be stopped and a phase III study would be required. The efficacy analysis for response was performed on data from protocol-qualified patients and assessable patients. The safety analysis was performed on data from all patients who received at least one dose of the study drug. Time to progression, overall survival and response duration were evaluated with Kaplan–Meier non-parametric methods using JMP® Software (SAS®, Cary, NC, USA) (see Fig. 2).

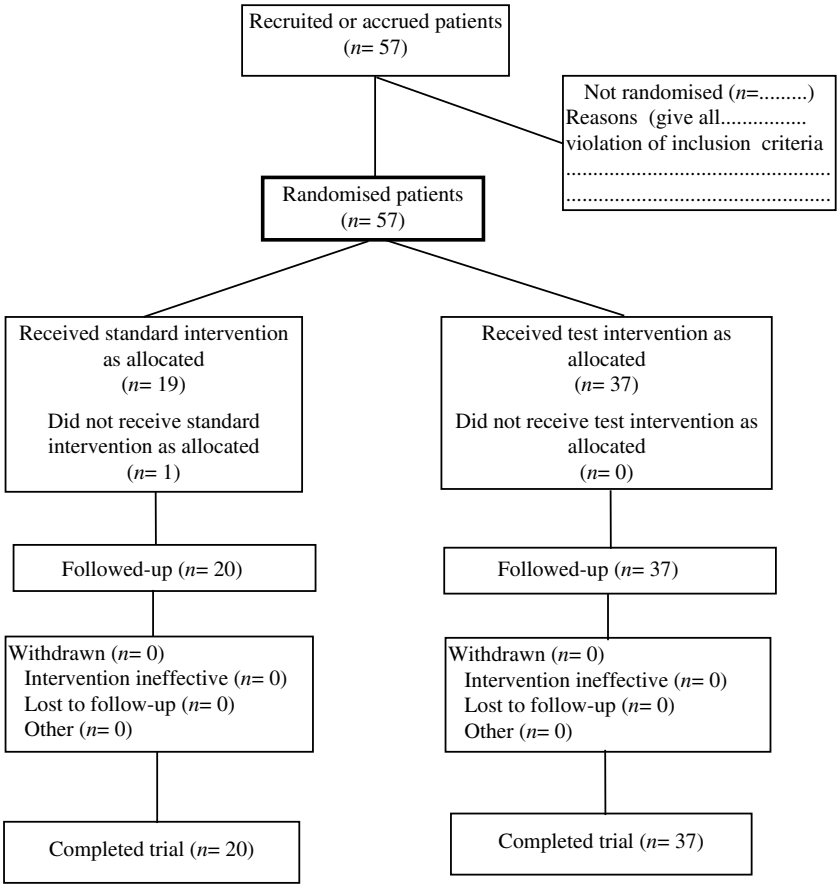

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. JAMA 1996, **276**, 637–39).

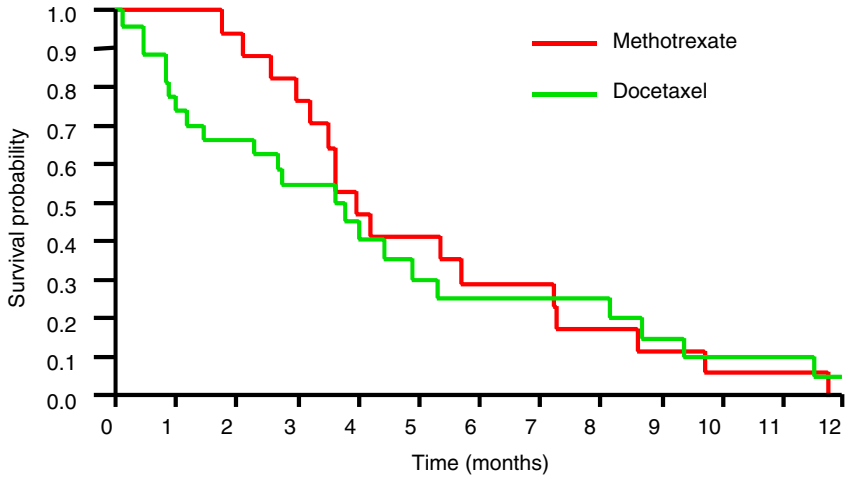

Fig. 2. Kaplan–Meier overall survival analysis.

4. Results

4.1. Patient characteristics

Between May 2000 and October 2003, 57 patients entered the study. One patient, randomised to receive methotrexate, died suddenly before receiving the first treatment. An additional patient was included in the methotrexate arm to obtain 20 assessable patients. Among the 57 included patients, 37 patients were randomised to receive docetaxel and 20 to receive methotrexate. There were 49 males and 8 females,

Table 1
Patient's characteristics

	Docetaxel	Methotrexate
Number of patients	37	20
Age (years)		
Median (range)	57 (43–81)	56 (44–70)
Gender		
Male	32	17
Female	5	3
Performance status (ECOG)		
Median (range)	1 (0–2)	1 (0–2)
Primary tumour site		
Oral cavity	12	3
Oro-pharynx	10	7
Hypo-pharynx	8	6
Larynx	6	3
Other	1	1
Site of recurrence		
Local recurrence	19	9
Distant metastasis	18	11
Disease-free interval (months)		
Median (range)	8 (1–53)	9 (2–61)
Primary tumour treatment		
Radio-chemotherapy	22	7
Chemotherapy	8	2
Radiotherapy	8	12
Surgery	4	10

median age was 59 years (range: 43–81 years), most patients had a performance status (PS) of 0 or 1. Twenty-eight patients (49%) relapsed within nine months following initial treatment and the recurrence occurred after more than nine months in other 29 patients (51%). The interval between the completion of the initial treatment and the relapse ranged between 0 and 165 months, with a median interval of 7.9 months. A local-regional recurrence alone and metastatic disease were observed in 28 and 29 patients, respectively. Patients characteristics are summarised in Table 1.

4.2. Toxicity

The haematological and non-haematological toxic effects observed among the 57 assessable patients are listed in Tables 2 and 3, respectively. The most common haematological toxicity with docetaxel was anaemia with grade 3–4 toxicity occurring in 19% of patients. Grade 3–4 neutropenia was observed in 12.5% of patients and was related to the occurrence of febrile neutropenia in two patients. No patient died due to neutropenic sepsis. The most common non-haematological toxicity was grade 3 ungueal toxicity which was observed in 9% of patients and required interruption of the treatment. Mucositis was the only other severe grade 3 or higher non-haematological toxicity reported (grade 3–4; 9%).

In patients treated with methotrexate, one patient presented with grade 4 haematological toxicity on the three blood cell lines. Grade 3 anaemia was the only other grade 3–4 haematological toxicity which occurred in 15% of patients. Other severe grade 3–4 non-haematological toxicities rarely occurred: 5% of diarrhoea and mucositis.

Table 2
Worst grade of haematological toxicity by patients, in percentage, by treatment arm

	Docetaxel (%)	Methotrexate (%)
	37 patients	20 patients
Neutropenia		
Grade 1–2	6	10
Grade 3–4	12.5	5
Anaemia		
Grade 1–2	25	10
Grade 3–4	19	15
Thrombocytopenia		
Grade 1–2	0	0
Grade 3–4	0	0

Table 3
Worst grade of non-haematological toxicity by patients, in percentage, by treatment arm

	Docetaxel (%)	Methotrexate (%)
	32 patients	20 patients
Nausea-vomiting		
Grade 1–2	16	5
Grade 3–4	0	0
Mucositis		
Grade 1–2	28	30
Grade 3–4	9	5
Diarrhoea		
Grade 1–2	19	5
Grade 3–4	0	5
Neurological		
Grade 1–2	19	0
Grade 3–4	0	0
Alopecia		
Grade 1–2	3	5
Grade 3–4	9	0
Ungueal		
Grade 1–2	0	0
Grade 3–4	9	0
Cutaneous		
Grade 1–2	19	42
Grade 3–4	0	0
Oedema		
Grade 1–2	9	0
Grade 3–4	0	0
Constipation		
Grade 1–2	9	5
Grade 3–4	0	0

4.3. Response and survival results

Among the 57 patients included, one patient in the methotrexate arm died before the first evaluation and

Table 4
Activity results

	Docetaxel	Methotrexate
	37 patients	20 patients
Objective response	27% (95% CI: 21.7–32.3%)	15% (95% CI: 11.2–18.8%)
Stable disease	13.5%	25%
Progressive disease	59.5%	60%
	Months (range)	Months (range)
Response duration	8.6 (1.7–17.6)	6.2 (2.8–10.6)
Time to progression	1.97 (1–19)	1.5 (1–12)
Overall survival	3.7 (0.13–19)	3.9 (0.2–11.8)

CI, Confidence interval.

was considered to have progressive disease. Confirmed ORs were observed in 10 of the 37 patients treated with docetaxel, giving a 27% response rate (95% Confidence Interval (CI): 21.7–32.3%); one patient had a complete response (CR) and 9 patients presented with a partial response (PR). Three of the 20 patients treated with methotrexate had an OR giving a 15% response rate (95% of CI: 11.2–18.8%) with a CR in one patient. The duration of response ranged between 2.8 and 10.6 months and 1.7 to 17.6 months in patients treated with methotrexate and docetaxel, respectively. Stable disease was observed in 5 (13.5%) and 5 (25%) patients in the docetaxel and methotrexate groups, respectively. Twenty-two patients (59.5%) had a progressive disease as their best response in the docetaxel group versus 12 patients (60%) in the methotrexate group (Table 4).

At the time of data collection, nine of the 57 patients enrolled were alive, leading to a 15.8% censored rate. Median overall survival was 3.7 months (range: 0.13–19 months) in the docetaxel group, versus 3.9 months (range: 0.2–11.8 months) in the methotrexate arm (Fig. 1). The median time to progression was 1.97 months (range: 1–19 months) and 1.5 months (range: 1–12 months) for the docetaxel and methotrexate groups, respectively (Log rank: $P = 0.45$).

5. Discussion

This study was undertaken to evaluate the activity of single agent docetaxel in patients with recurrent head and neck cancer using a control group treated with methotrexate to validate the results.

In patients with recurrent head and neck cancer, a weekly dose of 40–50 mg/m^2 of methotrexate provides response rates ranging between 8% and 16% in randomised studies [3–5]. In the present study, the 15% ORR in the methotrexate treatment group was similar to that reported in randomised trials which used methotrexate as a control arm. Despite this low efficacy rate, methotrexate being well tolerated, it is still considered as a major option for second and even first-line chemotherapy by the oncology community. All the recent investigational agents that have been compared with methotrexate have failed to demonstrate any benefit in terms of response rate, time to progression and overall survival (edatrexate [11], paclitaxel [12], nolatrexed [13] and S16020 [14]).

The results of this study have shown that patients treated with docetaxel and methotrexate had an overall survival of 3.7 versus 3.9 months and time to progression of 1.97 versus 1.5 months, respectively. Toxicity was higher in the docetaxel arm, in particular haematological toxicities, febrile neutropenia and ungueal toxicity (9%).

However, the high activity of single agent docetaxel, with a 27% response rate being observed, is of note, particularly given the anatomical localisation of head and neck cancers and consequent benefits of tumour reduction. A phase III trial is necessary to see if this high response rate translates into survival benefit for docetaxel use.

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