EUROPEAN JOURNAL OF CANCER 42 (2006) 200–204

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

A study from the EORTC new drug development group: Open label phase II study of sabarubicin (MEN-10755) in patients with progressive hormone refractory prostate cancer

W. Fiedler[a,*], N. Tchen[b], J. Bloch[c], P. Fargeot[d], R. Sorio[e], J.B. Vermorken[f], L. Collette[g], D. Lacombe[g], C. Twelves[h]

[a]Department of Medicine II, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20251 Hamburg, Germany
[b]Regional Cancer Center, Institute Bergonie, Bordeaux, France
[c]Department of Oncology, CHU Pitié-Salepétrière, Paris, France
[d]Department of Oncology, Centre Georges-Francois Leclerc, Dijon, France
[e]Division of Medical Oncology II, Centro di Riferimento Oncologico, Aviano, Italy
[f]Department of Medical Oncology, Universitair Ziekenhuis Antwerpen, Edegem, Belgium
[g]EORTC New Drug Development Programme (NDDP)/Data center, Brussels, Belgium
[h]St. James University Hospital, Leeds, UK

ARTICLE INFO

Article history:
Received 5 July 2005
Accepted 7 July 2005
Available online 7 December 2005

Keywords:
Hormone-refractory prostate cancer
PSA
Sabarubicin
MEN-10755
Phase II

ABSTRACT

Sabarubicin (MEN-10755), a new synthetic anthracycline analogue, was evaluated for safety and efficacy in a multicentre phase II study in patients with advanced hormone refractory prostate cancer (HRPC). Thirty seven patients were included, of which 34 were evaluable for PSA response according to Bubley's criteria. Sabarubicin was administered as a short (30 min) intravenous infusion at a dose of 80 mg/m^2 every 3 weeks. The main toxicity consisted of grade 3/4 neutropenia in 24 patients (64.9%), with grade 3/4 febrile neutropenia occurring in one patient only. Grade 3/4 cardiotoxicity was observed in 4 patients including one ineligible. Other toxicities were mild. Nine patients achieved a PSA response (26.5%), 10 patients had stable disease (29.4%) and 14 patients disease progression (41.2%). One patient (2.9%) had a PSA response that was not confirmed by repeat PSA testing. The objective response rate according to RECIST criteria was 6.7% in 15 patients with measurable disease. The median duration of PSA responses was relatively long 7.1 months (95% CI 4.9–20.7) as was the median time to treatment progression in patients with stable disease. The median overall survival was 18.7 months (95% CI 9.1–*N*), comparable to results recently observed in taxotere-containing regimens. To confirm and extend these results, further testing of sabarubicin in larger trials is warranted.

1. Introduction

Advanced prostate cancer is first treated by hormonal ablation. The median response duration of anti-androgen therapy is 12–16 months [1]. Once prostate cancer has become refractory to hormonal manipulation, the efficacy of subsequent therapy is unsatisfactory [2]. For many years anthracyclines, such as mitoxantrone combined with prednisone, have been

* *Corresponding author.*
E-mail address: fiedler@uke.uni-hamburg.de (W. Fiedler).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.07.030

regarded as the standard therapy for these patients [3]. Recently, two large randomized trials showed that treatment with taxanes used in combination with prednisone and/or estramustine phosphate increases median survival by about two months as compared with mitoxantrone/prednisone [4,5]. However, despite these advances, the evaluation of new agents in hormone-refractory prostate cancer is needed.

Sabarubicin (MEN-10755) is a new synthetic anthracycline analogue and it acts more as a topoisomerase II inhibitor than doxorubicine, because it causes DNA fragmentation at lower intracellular concentrations. Sabarubicin has been tested on human tumour xenografts and has shown activity against doxorubicine sensitive and resistant cell lines including breast and prostate cancer lines [6]. Sabarubicin has been evaluated by the EORTC in two phase I studies utilizing different administration schemes [7–9]. In one of them, a three weekly schedule was tested [8] and the recommended dose selected for phase II testing was 80 mg/m^2 with neutropenia being the dose limiting toxicity. In the present study, sabarubicin was evaluated at the same dose for activity and toxicity in patients with hormone refractory prostate cancer (HRPC).

2. Patients and methods

2.1. Patient selection

Patients were eligible if they had histologically proven prostatic adenocarcinoma, which was hormone refractory according to Bubley's criteria [10]. Patients had to have progressed under prior hormonal treatment with luteinizing hormone-releasing hormone (LH-RH) analogues or orchiectomy and anti-androgens, given either together or consecutively. Patients were required to have a continued elevation of PSA for at least 6 weeks after discontinuation of anti-androgens prior to study registration and a PSA value $\geqslant$5 ng/ml (HYBRITECH equivalent) within 2 weeks prior to registration. Patients without surgical castration had to have a serum testosterone level less than 50 ng/ml before study entry and to continue on LH-RH agonist therapy. Prior chemotherapy with estramustine or radiotherapy was allowed but had to be discontinued at least 4 weeks prior to study entry. Patients had to have an ECOG performance status $\leqslant$2. A history of severe heart disease, (especially no history of myocardial infarction in the previous six months), or cardiac insufficiency was not permitted. Normal cardiac functions documented by MUGA scan and 12 lead ECG were required. No concurrent treatment with other experimental drugs was allowed. Written informed consent was obtained from each patient before registration. The study was approved by the ethics committee of each participating centre according to national and local regulations.

2.2. Treatment plan

At enrolment, patients were evaluated by complete history; physical examination; performance status; vital sign recording; complete blood count; serum chemistries; and ECG and MUGA scan. For disease staging, a PSA test, bone scan and CT scans of measurable disease were required. MUGA scans were repeated every two cycles. Patients received sabarubicin at a dose of 80 mg/m^2 as a 30 min infusion every 3 weeks. Treatment could be continued until disease progression, but had to be stopped in case of patient's refusal, excessive toxicity precluding further therapy or patient's best interest according to the treating physician. Toxicity was recorded at every cycle and graded according to the NCI-CTC version 2.0 criteria. Response was evaluated every two cycles by PSA measurements and by CT scans if measurable disease was present. PSA responses, as defined by the Bubley criteria, required at least a 50% reduction of baseline PSA and a confirmation after at least 4 weeks [10]. Responses of measurable disease were evaluated according to RECIST criteria [11]. The sample size was calculated according to Simon 2-stage minimax design. In the first stage, 18 patients had to be entered. If at least one patient had PSA response, the cohort was to be increased up to 32 patients. A minimum of three responses in 32 patients were needed to claim activity. An overshoot in patient accrual in this multicentre setting was permitted to compensate for possible drop-outs. This study design ensures that, if the drug is active in 20% or more of the patients, the chance of erroneously rejecting the drug from further study is smaller than 10% and that if the drug is active in only 5%, the chance of erroneously concluding that the drug warrants further study is also smaller than 10%.

3. Results

3.1. Patient characteristics and treatment administration

Between October 2001 and March 2003, 37 patients were entered into the study. Three patients had to be excluded due to prior systemic chemotherapy with anthracycline or taxane containing regimens [1] or reduced baseline cardiac function [2]. Thirty four patients were eligible. They had a median age of 67 years (range 49–79 years). Additional patient

Table 1 – Baseline patients' characteristics

Number of evaluable Pts.	34
Median age (yr. range)	67 (49–79)
Performance status (WHO)	
0	14
1	18
2	2
Prior therapies	
Prostatectomy	13
Radiotherapy	24
Estramustine	14
Concomittant anti-androgen therapy	
LH-RH analogues	31
Castration	3
Tumour assessment	
PSA only	1
PSA and bone metastases	22
PSA and visceral metastases	11
Measurable disease	
Primary tumour	1
Lymph nodes	7
Lung metastases	1
Liver metastases	4
Other	6

Table 2 – Sabarubicin exposure (evaluable patients)

Median number of cycles	3.5
Number of cycles	No. of pts.
2	15
3	2
4	1
5	3
6	6
7	1
8	1
9	2
13	1
14	1
19	1
Median relative dose intensity % (range)	98.6 (76.3–107.7)
Dose reduction (No. of pts.)	3
Delays of dosing (No. of pts.)	12

Table 3 – Cumulative non-cardiac toxicities for all included patients (n = 37)

Worst related toxicity over all cycles (generic categories)		
N = 37 (%)	Grade > 0	Grade 3–4
WBC	32 (86.5)	14 (37.8)
Neutrophiles	36 (97.3)	24 (64.9)
Hemoglobin	31 (83.8)	3 (8.1)
Platelets	7 (18.9)	2 (5.4)
Allergic reaction	2 (5.4)	0 (0.0)
Cardiotoxicity	12 (32.4)	4 (10.8)
Constitutional symptoms	21 (56.8)	0 (0.0)
Skin/dermatology	20 (54.1)	0 (0.0)
Gastro-intestinal	26 (70.3)	1 (2.7)
Hemorrhage	2 (5.4)	1 (2.7)
Infection/febrile neutropenia	2 (5.4)	1 (2.7)
Neurotoxicity	9 (24.3)	0 (0.0)
Pulmonary	4 (10.8)	1 (2.7)
Pain	3 (8.1)	0 (0.0)

characteristics are displayed in Table 1. A median of 3.5 cycles (range 2–19) were administered (Table 2). The median relative dose intensity was 98.6% (range 76.3–107.7). Dose reductions were necessary in 3 patients and delays in dosing in 12 patients (in 9 patients due to toxicity).

3.2. *Toxicity*

The most frequent toxicity was haematological with grade 3/4 leucopenia in 14 patients (37.8%) and neutropenia grade 3/4 in 24 patients (64.9%). However, febrile neutropenia was rare and occurred only in one patient (2.7%). Grade 3/4 anaemia and thrombocytopenia were observed in only 2 (5.4%) and 3 patients (8.1%), respectively.

Cardiac function was monitored extensively in this study. MUGA scans were performed in all 37 patients and repeated every 2 cycles. Related cardiac abnormalities were identified in 12 patients including one in an ineligible patient. In eligible patients with normal baseline cardiac status, 8 patients had grade 1/2 and 3 patients had grade 3/4 toxicities. These included 2 patients with decreased left ventricular ejection fraction by MUGA scan; 2 patients with supraventricular tachycardia and one with sinus tachycardia; one patient with right bundle branch block; one patient with ventricular extrasystoles; one with systolic murmur caused by anaemia; one with hypertension and decrease of ejection fraction measured by MUGA scan; and one with hypotension. The only cardiotoxicity grade 4 in the eligible patient group consisted of pulmonary embolism after 2 cycles of therapy. There was also one grade 4 cardiac toxicity in an ineligible patient consisting in congestive cardiac failure. Cardiac abnormalities were documented to have resolved in 5 patients.

In addition to the 3 cases with decrease of left ventricular ejection fraction (LVEF) reported above, another 6 patients were observed to have decreased LVEF by MUGA scan that was scored as not clinically relevant. Of these 6 patients, 2 were ineligible due to already impaired LVEF at entry on study.

Additional systemic toxicities were infrequent and usually mild and antiemetics were given for symptomatic nausea or vomiting in only 8 patients (23.5%). Toxicity is summarized in Table 3.

3.3. *Anti-tumour activity*

Thirty-four patients were evaluable for PSA response according to the Bubley criteria [10]. Fifteen patients had measurable disease and could be followed for objective tumour response [11]. Of the 34 patients, 9 (26.5%) had a confirmed PSA response (95% CI: 12.9–44.4%). One patient had an unconfirmed PSA response (2.9%). Ten patients had stable disease (29.4%) and 14 patients had disease progression (41.2%). The median duration of PSA response was 7.1 months (95% CI: 4.9–20.7 months, Fig. 1A). For the 10 patients with stable disease, PSA progression was not observed during the observation period in 8 patients. Time to first PSA progression of the whole group of 34 patients was 4.2 months (95% CI: 1.4–9.4 months) (see Fig. 1B).

Of the 15 patients with measurable disease, one patient had partial remission (6.7%), 7 had stable disease (46.7%), 5 had disease progression (33.3%) and two were not re-assessed (13.3%) post-baseline evaluation. The duration of the partial remission was 8 months. The median duration of stable disease has not been reached. At one year, 51.4% of patients with objective stable disease had not progressed (95% CI: 11.8–81.3%).

The median survival for the whole group of 34 patients was 18.7 months (95% CI: 9.1–*N*, Fig. 1C).

4. Discussion

In the current study, the activity and toxicity profile of sabarubicin administered at a dose of 80 mg/m^2 as a short (30 min) intravenous infusion every 3 weeks was evaluated in patients with advanced HRPC. In general, chemotherapy was well tolerated and could be easily given in an out-patient setting. The most frequent toxicity was haematological with grade 3/4 neutropenia occurring in 64.9% of patients but neutropenic fever was observed in only 1 of 34 patients.

Impairment of cardiac function is a potential toxicity of all anthracyclines. The cardiotoxicity of anthracyclines such as doxorubincin, epirubicin or idarubicin varies considerably with the administered total dose, and has been attributed to the generation of metabolites with alcohol residues [12,13]. The degree to which these toxic metabolites are formed

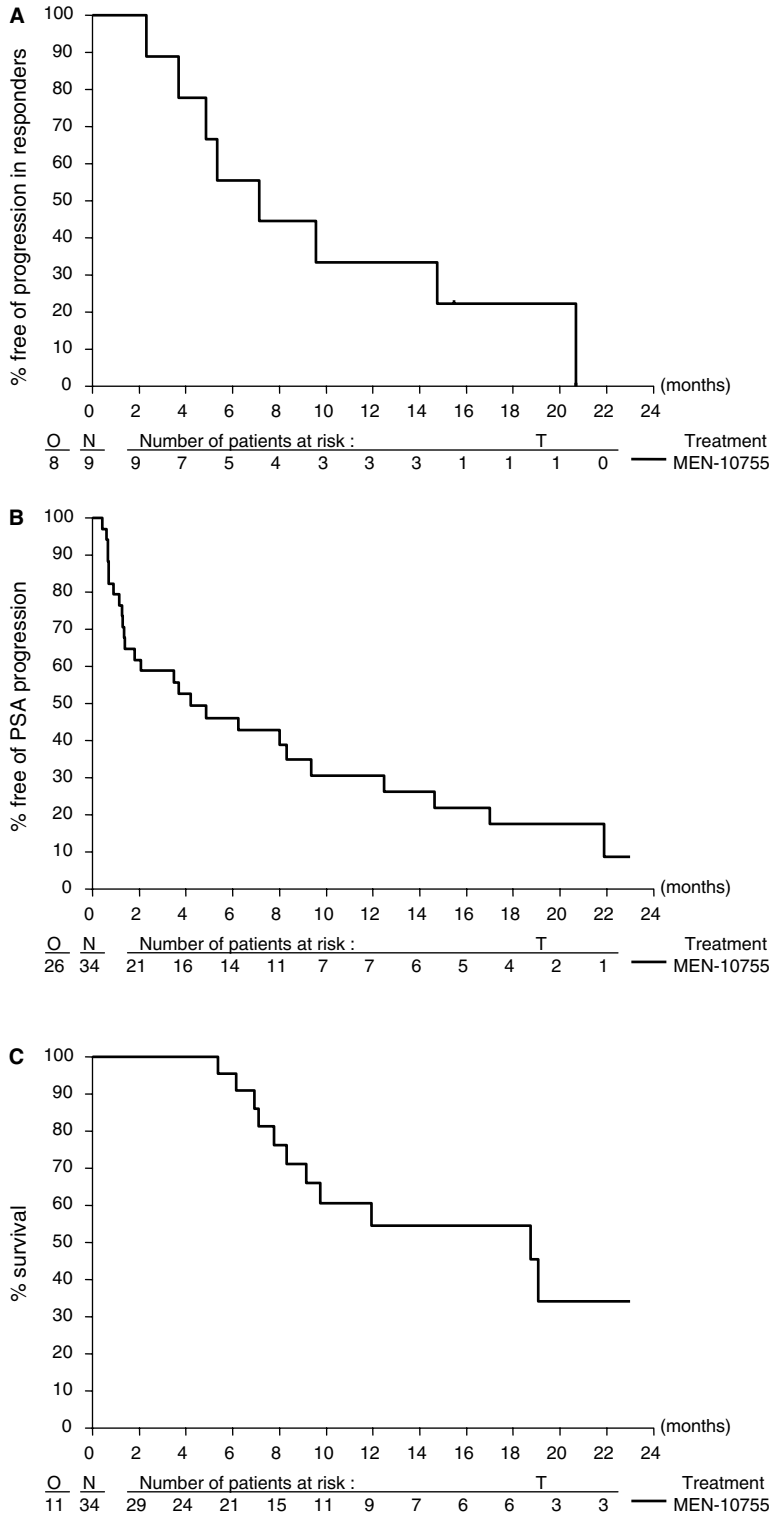

Fig. 1 – (A) Duration of PSA response with partial PSA response according to Bubley's criteria. (B) Time to first PSA progression of all 34 evaluable patients. (C) Overall survival for all 34 evaluable patients.

depends on the parent anthracycline compound. In preclinical models, sabarubicin has been shown to cause less cardiotoxicity than doxorubicin and even than epirubicin [14]. Therefore in the present study, continued therapy with sabarubicin in non-progressing patients was permitted over the sixth cycle under close clinical observation and with MUGA scans being performed after every second cycle for objective assessment of cardiac function. Sabarubicin showed to be well tolerated and seven patients received more than six cycles of therapy. The maximum number of administered cycles was 19. In the 34 evaluable patients, 7 cases of grade 1–2, 2 cases of grade 3 and one case of grade 4 cardiotoxicity

(pulmonary embolism) were observed. However, a closer correlation between the cumulative sabarubicin dose administered to the occurrence of cardiac toxicity and/or its severity was not detected in this study. These observations imply that sabarubicin retains some potential cardiotoxicity which needs to be further defined in trials with larger patient numbers in order to determine a safe cumulative dose limit.

The present early phase II trial followed the Simon design and was powered in order to not miss a response rate of 20% with an error of 10%. The PSA response was determined according to Bubley's criteria [10]. The observed confirmed PSA response rate was 26.5% (9/34 patients). Therefore, the study drug showed sufficient activity and further testing in larger trials is recommended.

In two recent randomized studies taxotere combined with prednisone was established as a new standard for the treatment of HRPC [4,5]. In these trials, the PSA response rates were higher than in our study with a response rate of 50% and 48%, respectively. However, in the present study, the duration of partial response and stable disease during continued treatment with sabarubicin were relatively long with median overall survival of 18.7 months and is comparable to the median survival in the taxotere arms of both studies with 17.5 and 18.9 months, respectively. Although these promising results could be conditioned by the relatively small dimension of the present study, a larger trial comparing sabarubicin single agent with a taxotere combination seems warranted. The results shown by sabarubicin in advanced HRPC patients may provide the rationale for introducing a new anthracycline drug in chemotherapy regimens for this disease.

Conflict of interest statement

None declared.

Acknowledgements

This study was supported by Menarini Ricerche SpA, Florence, Italy, Benedicte Marchal, Data Management EORTC Data Centre.

REFERENCES

1. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;**321**(7):419–24.
2. Beedassy A, Cardi G. Chemotherapy in advanced prostate cancer. *Semin Oncol* 1999;**26**(4):428–38.
3. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999;**17**(8):2506–13.
4. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;**351**(15):1513–20.
5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;**351**(15):1502–12.
6. Pratesi G, De Cesare M, Caserini C, et al. Improved efficacy and enlarged spectrum of activity of a novel anthracycline disaccharide analogue of doxorubicin against human tumour xenografts. *Clin Cancer Res* 1998;**4**(11):2833–9.
7. Bos AM, de Vries EG, Dombernovsky P, et al. Pharmacokinetics of MEN-10755, a novel anthracycline disaccharide analogue, in two phase I studies in adults with advanced solid tumours. *Cancer Chemother Pharmacol* 2001;**48**(5):361–9.
8. Roelvink M, Aamdal S, Dombernovsky P, et al. Phase I study of MEN-10755 in patients with a solid tumour as a short i.v. infusion given once every 3 weeks. *Eur J Cancer* 1999;**35**(Suppl. 4):289.
9. Schrijvers D, Bos AM, Dyck J, et al. Phase I study of MEN-10755, a new anthracycline in patients with solid tumours: a report from the European Organization for Research and Treatment of Cancer, Early Clinical Studies Group. *Ann Oncol* 2002;**13**(3):385–91.
10. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;**17**(11):3461–7.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–16.
12. Minotti G, Licata S, Saponiero A, et al. Anthracycline metabolism and toxicity in human myocardium: comparisons between doxorubicin, epirubicin, and a novel disaccharide analogue with a reduced level of formation and 4Fe–4S reactivity of its secondary alcohol metabolite. *Chem Res Toxicol* 2000;**13**(12):1336–41.
13. Minotti G, Parlani M, Salvatorelli E, et al. Impairment of myocardial contractility by anticancer anthracyclines: role of secondary alcohol metabolites and evidence of reduced toxicity by a novel disaccharide analogue. *Brit J Pharmacol* 2001;**134**(6):1271–8.
14. Sacco G, Giampietro R, Salvatorelli E, et al. Chronic cardiotoxicity of anticancer anthracyclines in the rat: role of secondary metabolites and reduced toxicity by a novel anthracycline with impaired metabolite formation and reactivity. *Brit J Pharmacol* 2003;**139**(3):641–51.