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Treatment with docetaxel and cisplatin in advanced adrenocortical carcinoma, a phase II study

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Background: Adrenocortical carcinoma (ACC) is a rare disease with a poor response to chemotherapy. Cisplatin is the most widely investigated drug in the treatment of ACC and *in vitro* studies have indicated activity of taxanes. The objectives of this study were to evaluate the efficacy and toxicity of cisplatin combined with docetaxel as first-line treatment of advanced ACC.

Methods: Patients with advanced ACC were included in this phase II trial investigating the response to a combination of cisplatin (50 mg m^{-2}) and docetaxel (60 mg m^{-2}) administered with a 3-week interval.

Results: Nineteen patients were included in this study. The response rate was 21% (95% CI: 3–39%). No patients obtained a complete response, 32% had stable disease, and 37% progressed while on treatment. The median progression-free survival (PFS) was 3 months (95% CI: 0.7–5.3 months) and 1 year PFS was 21% (95% CI: 3–39%). Median survival was 12.5 months (95% CI: 6–19 months). The predominant grade 3/4 toxicity was neutropenia (35%); febrile neutropenia occurred in 5% of cycles.

Conclusion: This study could not demonstrate that the combination of cisplatin and docetaxel has higher efficacy than other regimens reported in previous studies.

Adrenocortical carcinoma (ACC) is a rare malignant tumour with an annual incidence of 0.7–2.0 per 1 million population-years (Kebebew *et al*, 2006; Golden *et al*, 2009). The majority of patients have locally advanced (ENSAT stage III) or metastatic disease (stage IV), not suitable for radical surgery. The prognosis of stage IV ACC patients is dismal, with a 5-year survival rate of $<15\%$ (Icard *et al*, 2001; Berruti *et al*, 2005; Lughezzani *et al*, 2010). Different chemotherapy regimens have shown low response rates (RR) and short duration of response in retrospective studies and small phase II studies (Fassnacht *et al*, 2011; Costa *et al*, 2011). Recently, a large phase 3 trial (FIRM-ACT) comparing the combination of etoposide, doxorubicin and cisplatin (EDP) plus mitotane, with a combination of streptozocin and mitotane has been published. The EDP group had a higher RR (23.2% *vs* 9.2%, $P<0.0001$) and longer median progression-free survival (PFS) (5.0 months *vs* 2.1 months; hazard ratio (HR): 0.55; 95% confidence interval (CI): 0.43–0.69; $P<0.0001$); however, there was no significant difference in median duration of overall survival (OS) (14.8 months *vs* 12.0 months; HR: 0.79; 95% CI: 0.61–1.02; $P=0.07$) (Fassnacht *et al*, 2012).

The aim of the present prospective phase II study was to examine the response of a combination of cisplatin, which is the most widely tested cytotoxic agent in ACC, and docetaxel, a drug which has shown to be effective in different human ACC cell lines (Fallo *et al*, 1996; Fallo *et al*, 1998; Montoya *et al*, 2008).

PATIENTS AND METHODS

Patients. Patients with histologically confirmed diagnosis of locally advanced, inoperable and/or metastatic ACC were eligible. Further inclusion criteria comprised performance status (PS) $\leqslant 2$, expected survival of >12 weeks, measurable disease as stated in Response Evaluation Criteria in Solid Tumours (RECIST 1.0) and age 18–75 years. Other inclusion criteria included Cr-EDTA clearance >60 ml min^{-1}, neutrophil count $>1.5\times10^{9}$ per l,

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platelet count $>100 \times 10^9$ per l, bilirubin <1.5 ULN and aspartate aminotransferase or alanine aminotransferase <3 ULN. Patients were not eligible if they had received any prior chemotherapy, radiotherapy or immunotherapy within the previous 4 weeks before inclusion. Other exclusion criteria included known neuropathy $\geqslant$grade 2 according to National Cancer Institute-Common Toxicity Criteria version 3.0 (NCI-CTC v 3.0), other contemporary experimental treatment, any serious disorder incompatible with trial participation, other known malignant disease within the previous 5 years (apart from non-melanoma skin cancer and carcinoma *in situ* cervix uteri).

Treatment. The regimen consisted of cisplatin, 50 mg m^{-2} given intravenously on day 1; docetaxel at a dose of 60 mg m^{-2} given intravenously on day 1, administered every 3 weeks. Dose modification for toxicity for each of the drugs was pre-specified in the protocol.

Response evaluation. Response assessment by CT scan was carried out by comparing with baseline, after every second cycle and 3–4 weeks after end of treatment. An experienced radiologist reviewed the CT scans and assessed the response according to RECIST 1.0 criteria. PFS was defined as the time from first day of treatment to disease progression or death. Overall survival was measured from initiation of treatment.

Study design and statistics. This phase II trial was designed in two stages, based on Simon's two-stage design. The treatment programme was designed to assess the activity of the regimen as an at least 30% response rate (RR) with a significance level of 0.05 and a power of 80%. If <7 of 19 patients had a PR, the trial was to be halted. Otherwise, 20 more patients were to be included for treatment.

The primary end point was objective RR. Secondary end points were toxicity according to NCI-CTC v 3.0, PFS and OS.

The study was conducted according to the ethical principles of the Declaration of Helsinki and WHO Good Clinical Practice and was approved by the Danish Medicines Agency and by the regional Ethics Committee. Trial monitoring was carried out by an independent regional GCP unit. The trial is registered with ClinicalTrials.gov as NCT00324012.

RESULTS

Patients. Twenty-one patients with histologically confirmed ACC were recruited from March 2005 to July 2011. Two patients were excluded from the analysis: one patient was diagnosed with perforated diverticulitis before any study-specific intervention, whereas the second patient was excluded because PS decreased from 2 to 3 before any study-specific intervention.

Baseline characteristics of the remaining 19 patients are summarised in Table 1.

Tumour response and survival analysis. Computed tomography scans of all 19 patients with measurable disease showed a PR according to RECIST criteria in 4 patients (21%, 95% CI: 3–39%). No patients had CR. In 6 patients (32%, 95% CI: 11–53%) imaging revealed s.d., whereas 7 patients (37%, 95% CI: 15–59%) progressed while on treatment. The median PFS for patients who had PR was 9.4 months (range 3.3 months to 17.8 months). Two patients were not evaluable for response: one patient developed sepsis complicated by renal failure without neutropenia during the first cycle of treatment. This patient never recovered from renal failure (grade 3), which made further cisplatin treatment impossible. The other patient was physically unfit for the second cycle and could not be evaluated.

The median duration of PFS was 3 months (95% CI: 0.7–5.3 months) and 12 months PFS was 21% (95% CI: 3–39%). At 12 months, 47% of patients (95% CI: 25–69%) were alive. Median duration of survival was 12.5 months (95% CI: 6–19 months) (Table 2). Seven patients are still alive with a median follow-up of 15.3 months (range 2–44.8 months).

Table 1. Patient characteristics ($n=19$)

Characteristic	*n* (%)
Sex	
Male	9 (47)
Female	10 (53)
Age (years)	
Median (range)	50 (22–70)
Performance status	
0	3 (16)
1	12 (63)
2	4 (21)
ENSAT tumour stage	
IV	19 (100)
Site of tumours	
Adrenal gland + other viscera	7 (37)
Adrenal gland + lymph nodes	1 (5)
Lymph nodes only	2 (11)
Other viscera only	7 (37)
Other viscera + lymph nodes + adrenal gland	2 (11)
Lung	14 (74)
Liver	8 (42)
No. of disease sites	
1	5 (26)
2	5 (26)
>2	9 (47)
Endocrine symptoms	
Cushing's syndrome	9 (47)
No symptoms	10 (53)
Prior treatment	
Surgery	19 (100)
Radiotherapy	0
Mitotane[a]	5 (26)

[a]All patients treated with mitotane had progressive disease at the time of inclusion.

Table 2. Treatment response

Kind of response	*n* (%, 95% CI)[a]	Progression-free survival – median (range)
PR	4 (21, 3–39%)	9.4 (3.3–17.8)[b]
s.d.	6 (32, 11–53%)	5.3 (2.8–16)[c]
PD	7 (37, 15–59%)	NA

[a]Response was not evaluable in two patients.
[b]One patient is still without signs of progression 12 months after obtaining partial response.
[c]Two patients are still without signs of progression 12.8 months and 16 months after obtaining s.d.

Table 3. Treatment-related toxicity according to NCI-CTC v 3.0 (91 cycles in total)

	Grade 3 (%)	Grade 4
Haemoglobin	9 (10)	0
Leucocytes	24 (26)	11 (12%)
Platelets	1 (1)	1 (1%)
Febrile neutropenia	5 (5)	0
Vomiting	4 (4)	0
Mucositis/stomatitis	1 (1)	0
Neuropathy-sensory	3 (3)	0
Musculoskeletal pain	1 (1)	0
Fatigue	13 (14)	0
Hypomagnesemia	3 (3)	0
Hypokalemia	3 (3)	0
Hearing	1 (1)	0
Renal failure	1 (1)	0

Safety and tolerability. A total of 91 cycles with docetaxel and cisplatin were administered to 19 patients. Associated grade 3/4 toxic effects are reported in Table 3. The most frequent adverse effects were neutropenia (38% of cycles), fatigue (14% of cycles), anaemia (10% of cycles) and febrile neutropenia (5% of cycles).

DISCUSSION

Progress in medical treatment of patients with ACC has been dismal due to the low sensitivity to antineoplastic agents. This report describes the results of a phase II trial combining docetaxel and cisplatin. Objective RR was 21% (4 of 17 patients with measurable disease; 95% CI: 3–39%), and because we could not meet the protocol-defined precondition of 30% RR, the study was stopped. Response duration for patients with PR and s.d. was 9.4 months (3.3–17.8 months) and 5.3 months (2.8–16 months), respectively. Median PFS was 3 months (95% CI: 0.7–5.3 months).

As a whole, the combination of docetaxel and cisplatin was manageable. The most frequent adverse event was neutropenia. Febrile neutropenia, anaemia and fatigue were comparable to previous phase II studies using other combination chemotherapy regiments in ACC (Williamson *et al*, 2000; Abraham *et al*, 2002; Berruti *et al*, 2005) and the combination of doxetaxel and cisplatin in other malignancies (Specht *et al*, 2000; Atmaca *et al*, 2013). No grade 4 febrile neutropenia or treatment-related deaths were observed. Compared with previous phase II studies, efficacy of this combination regimen is equally disappointing. The recently published randomized phase 3 study using EDP plus mitotane *vs* streptozocin showed significantly higher efficacy in the EDP plus mitotane arm. For the EDP plus mitotane regimen, the RR was 23.2% (95% CI: 16.7–30.7%) and the median progression-free survival was 5 months (95 CI: 3.5–6.9 months). The FIRM-ACT study cannot be directly compared with our study, but the data indicate that the efficacy of EDP plus mitotane is comparable with the combination of docetaxel and cisplatin. Compared with EDP plus mitotane the combination of docetaxel and cisplatin had a comparable toxicity profile, though neurologic toxicity was more frequent in the combination of docetaxel and cisplatin.

In order to improve the treatment of this rare disease, we believe that the treatment should be done centrally in specialized multidisciplinary teams. In addition, clinical data and biobank material should be collected prospectively by a multinational group with the aim of investigating the biology of this heterogeneous disease in order to improve its treatment. Only through a multinational cooperation, further improvements in the treatment of ACC can be done.

In conclusion, combining docetaxel and cisplatin in ACC, cannot be recommended.

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