

CLINICAL STUDY

Bevacizumab plus capecitabine as a salvage therapy in advanced adrenocortical carcinoma

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Abstract

Objective: No standard therapy for advanced adrenocortical carcinoma (ACC) is established by any randomized trial but a consensus conference 2003 recommended mitotane as monotherapy or combined with etoposide, doxorubicin and cisplatin or with streptozotocin as first-line systemic therapy. However, there is no evidence for any therapy beneficial in patients failing these therapies. Therefore, we evaluated the effects of the anti-VEGF antibody bevacizumab plus capecitabine as salvage therapy in ACC.

Methods: Patients registered with the German ACC Registry with refractory ACC progressing after cytotoxic therapies were offered treatment with bevacizumab (5 mg/kg body weight i.v. every 21 days) and oral capecitabine (950 mg/m² twice daily for 14 days followed by 7 days of rest) in 2006–2008. Evaluation of tumour response was performed by imaging according to response evaluation criteria in solid tumours every 12 weeks.

Results: Ten patients were treated with bevacizumab plus capecitabine. None of them experienced any objective response or stable disease. Two patients had to stop therapy after few weeks due to hand-foot syndrome, and three patients died on progressive disease within 12 weeks. Other adverse events were mild (grade I–II). Median survival after treatment initiation was 124 days.

Conclusions: Bevacizumab plus capecitabine has no activity in patients with very advanced ACC. Hence, this regimen cannot be recommended as a salvage therapy.

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Introduction

Owing to the rarity of adrenocortical carcinoma (ACC), there is no treatment established by any randomized trial (1). Surgery is regarded as therapy of choice in all patients with resectable tumour, but 25% of patients already have distant metastases at the time of primary diagnosis and the majority of patients develop metastases even after assumed curative surgery (2–12). In 2003, an international consensus conference on the management of ACC recommended for patients with advanced metastatic disease mitotane as monotherapy or combined with etoposide, doxorubicin and cisplatin (13) or with streptozotocin (14) as first-line systemic treatment based on two phase II trials leading to an evidence level not better than 2 (1). The two latter regimens are currently compared in the first randomized trial in this disease (FIRM-ACT trial, www.firm-act.org). Up to now, more than 280 patients have been enrolled, but results will not be available before 2011 after analysis of 300 patients. Regarding second-line therapies, the consensus conference acknowledged that only anecdotal evidence is

available and recommended to use the aforementioned regimens that were not used as first-line. For patients failing these treatment regimens, no recommendations could be given and it is obvious that new treatment options are needed.

The initiation of the FIRM-ACT trial has led to a profound change in the care of patients with ACC in Germany (15). Since 2004, an increasing number of patients with ACC consult few specialized centres regarding treatment options. However, as expected from previous experience with cytotoxic chemotherapy, many patients fail both FIRM-ACT protocols or progress after initial response leading to an urgent demand for salvage therapy in these often young patients. The FIRM-ACT investigators in Germany (organized in the German Adrenal Network Improving Treatment and Medical Education (GANIMED) network) responded to this growing need by developing several defined salvage protocols for compassionate use in this patient group. These protocols were offered to clinicians caring for patients with progressive ACC registered in the German ACC Registry (www.nebennierenkarzinom.de;

Clinicaltrials.gov identifier: NCT00453674) allowing local investigators and the patient to choose between different options and to prospectively evaluate the response to therapy with the aim to identify new active treatment protocols. The aim of this standardization of therapeutic efforts in all GANIMED centres was to provide some evidence for potentially valuable treatment regimens in a relatively short period of time. These protocols were influenced by preclinical data concerning, e.g. receptor expression, theoretical considerations on tumorigenesis and promising advances in other carcinoma entities with limited prognosis.

Anti-angiogenic substances have been discussed in several reviews as an interesting option for advanced ACC (16–18). Although none of the clinically approved drugs have been tested in preclinical or clinical studies in ACC, there was some evidence that an anti-angiogenic approach might be of benefit for patients with ACC. The majority of more than 160 investigated ACC tumour samples showed specific staining against vascular endothelial growth factor (VEGF) and its most important receptor (VEGF receptor 2) in immunohistochemical analysis (unpublished data). Furthermore, elevated VEGF levels were reported in tumour samples and in serum of patients with ACC (19, 20). In addition, encouraging results in advanced colorectal (21), breast (22), lung (23) and renal (24) cancer were recently published showing significant prolongation of survival and good tolerance of bevacizumab, a monoclonal anti-VEGF antibody. Therefore, we adapted protocols of these entities for patients with advanced ACC. To enforce the power of the therapy regime, we combined bevacizumab with capecitabine, a prodrug of fluorouracil. Fluorouracil has been reported to have adrenolytic power on adrenal cancer cell lines (25). Whereas fluorouracil has to be given i.v., capecitabine has the charm of oral administration. In addition, trials in metastatic colorectal cancer have shown that capecitabine plus oxaliplatin (XELOX) is not inferior to standard fluorouracil plus oxaliplatin (26), and that bevacizumab in combination with XELOX significantly improved progression-free survival (27).

Here, we report on the treatment with bevacizumab and capecitabine on a compassionate use basis in ten patients with advanced ACC refractory to several cytotoxic chemotherapies.

Materials and methods

Patients

Between January 2006 and June 2008, physicians of the GANIMED network offered patients with advanced ACC treatment with bevacizumab and capecitabine when they fulfilled the following inclusion criteria: histologically proven ACC in an unresectable, locally advanced, recurrent or metastatic stage after progression despite treatment with mitotane and at least two cytotoxic chemotherapies including etoposide,

doxorubicin, cisplatin and streptozotocin. All patients had radiologically measurable target lesions as defined by response evaluation criteria in solid tumours (RECIST) criteria (28), were aged over 18 years, in acceptable clinical condition (Eastern Cooperative Oncology Group stage of 0–2) including adequate haematological, renal and hepatic function, and desired further treatment. Exclusion criteria were prior exposure to anti-VEGF antibody or capecitabine/fluorouracil, other malignancies within the last 5 years, or active infections. All patients were informed of the experimental nature of the treatment and signed informed consent.

Treatment protocol

Bevacizumab (Avastin, F Hoffmann-La Roche) was given intravenously every 3 weeks in a dosage of 5 mg/kg body weight as an infusion. Capecitabine (Xeloda, F Hoffmann-La Roche) was administered orally 950 mg/m² twice daily for 14 days followed by 7 days of rest. Dose of capecitabine was increased to 1250 mg/m² in case of good tolerance. In general, the therapy was carried out on an outpatient basis. Continuation of concomitant administration of mitotane was permitted in patients in whom some clinical benefit was assumed despite progression during prior mitotane treatment (e.g. in patients with Cushing's syndrome).

Evaluation

Baseline evaluations included a documentation of patient history, physical examination, and performance status. A complete blood cell count, serum chemistry profile (Na, K, Ca, PO₄, creatinine, glucose, aspartate aminotransferase (AST)/serum glutamate oxalacetate transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase, total bilirubin, albumin), and chest and abdominal computed tomography (CT) or magnetic resonance imaging scans were performed. This evaluation was repeated every 12 weeks, and tumour response was determined. Response was assessed using the RECIST (28). All radiological images were reviewed by the local radiologists and an independent radiologist who finally determined response. In case of progressive disease, it was recommended to stop treatment.

Drug-related adverse events and toxicities were recorded, according to the Common Toxicity Criteria of the National Cancer Institute (version 3.0).

Results

Patient characteristics

Ten patients (7 male and 3 female) with advanced ACC were treated with bevacizumab and capecitabine between May 2006 and June 2008. Patient's

Table 1 Patient characteristics and previous therapies.

Patient no.	Sex	Age (years)	Hormonal activity	Time from diagnosis of ACC to start of BC (months)	Time from diagnosis of metastasis to start of BC (months)	Number of previous surgeries	Prior systemic therapies (months)	Other prior therapies
1	Male	46	N	20	20	1	M (5), EDP-M (8), Sz-M (2), EG-M (3)	
2	Male	38	A	19	12	4	Sz-M (2), EDP-M (5), EG (3)	
3	Male	45	N	18	18	1	M (5), Th-M (4), EDP-M (4), Sz-M (4), EG-M (2)	RT skull
4	Male	45	N	20	20	2	Sz-M (4), EDP-M (2), EG-M (1)	
5	Male	50	N	16	12	1	M (3), EDP-M (4), Sz-M (2), EG-M (3)	
6	Female	73	A	32	32	1	M (2), Sz-M (6), EDP-M (10), EG-M (8), Su (3)	
7	Male	62	N	22	11	1	M (11), EDP-M (4), Sz-M (2)	
8	Female	46	C	22	22	4	M (4), Sz-M (8), M (3), EDP-M (2), Su-M (3)	CE liver, RT spin
9	Male	68	C	42	15	4	M (4), Sz-M (2), EDP-M (3)	
10	Female	42	A,C	48	27	2	M (1), EDP-M (5), Sz-M (3), EDC-M (3), Su-M (3)	RT lymph node

N, hormonally inactive or with no initial hormonal work-up; A, androgen excess; C, cortisol excess. BC, bevacizumab and capecitabine. Duration of prior systemic therapies is given in months in parentheses; M, mitotane mono; EDP-M, etoposide, doxorubicin, cisplatin, mitotane; EDC-M, etoposide, doxorubicin, carboplatin, mitotane; Sz-M, streptozotocin and mitotane; EG, erlotinib and gemcitabine; EG-M, erlotinib, gemcitabine, mitotane; Th-M, thalidomide, mitotane; Su-M, sunitinib, mitotane; Su, sunitinib; RT, radiotherapy; CE, chemoembolization.

characteristics including initial tumour stage, hormonal activity and previous surgical, radiological or medicinal therapies are given in Table 1. Median age was 46 years, and median time from diagnosis of distant metastases to start of therapy with bevacizumab plus capecitabine was 19 months. Most patients had a history of several surgeries, and all were heavily pretreated with systemic therapies. Median number of administered drug regimens was 4 (range 3–5; Table 1). Etoposide, doxorubicin and cisplatin plus mitotane as well as streptozotocin plus mitotane were administered in all patients (nine of them within the FIRM-ACT trial). Furthermore, six patients were pretreated with gemcitabine plus erlotinib (29), three with sunitinib and three with radiotherapy and chemoembolization necessary. Five patients had concomitant mitotane, because it was at the discretion of the local physician to continue with mitotane when some clinical benefit was presumed. In two patients, endogenous glucocorticoid excess was treated with metyrapone ($n=1$) and RU486 ($n=1$) respectively.

All patients had significant tumour burden with a median sum of longest diameter of the pre-specified target lesions of 205 mm (range 93–501 mm), and progressing disease was documented before initiation of bevacizumab plus capecitabine. Six patients had local recurrence, and all suffered from tumour manifestations in at least two different organs as shown in Table 2.

In all four patients, in whom tumour samples were stained with anti-VEGF antibody, expression of VEGF protein was detectable in the tumour cells.

Outcome

None of the ten patients experienced any objective response or stable disease during therapy with bevacizumab plus capecitabine. Three of them had already died due to progressive disease before first scheduled restaging at 12 weeks. Two patients (nos 1 and 4) experienced relevant hand-foot syndrome and had to stop therapy after 2 and 3 weeks respectively, without any detectable benefit. In patient no. 4, clear tumour progress was detectable at the time of stopping bevacizumab and capecitabine (Table 2).

The median increase in sum of the longest diameter of target lesions at the first staging was 57 mm (range –21 to 139 mm; Table 2, Fig. 1). Median survival without progression after starting bevacizumab/capecitabine was 59 days, and median overall survival was 124 days (Fig. 2). Only two patients had an increase in target tumour mass <25%. Patient no. 2 had stable target lesions after 12 weeks and benefited clinically from bevacizumab and capecitabine. Therefore, therapy was continued despite formally progressive disease due to two new metastases in liver and abdomen. However, after an additional 12 weeks, tumour had progressed tremendously (including multiple new metastases). Patient no. 10 was radiologically stable, but developed acute superior vena cava syndrome after 8 weeks requiring an emergency radiation therapy and was, therefore, judged as progressive disease.

With exception of the two cases of therapy limiting hand-foot syndrome, adverse events were minor and treatment was in general well tolerated. Particularly,

Table 2 Disease status and results of evaluation.

Patient no.	Sites of tumour manifestations	VEGF expression	Concomitant mitotane (maximum plasma level mg/l)	Cumulative dose of C (g)	Cycles of B	Sum (in mm) of the longest diameter (number of target lesions)			Number of new mets (1st staging)	Overall response	Treatment after BC	Survival since start BC (months)
						Baseline	1st staging	1st staging				
1	lr, ab, li, lu, hi	NA	12.7	112	1	97 (3)	125 (3)	3 lu	PD	vac	3	
2	lr, lu, mu, ab, ax	NA	No	308	6	129 (3)	132 (3)	2 ab, li	PD	su	9	
3	lr, li, lu, bo, ab	+	9.0	234	3	378 (10)	— ^a		PD	—	2	
4	ab, lu, mu	NA	10.6	56	1	200 (6)	306 (6)	1 li	PD	vac	4	
5	lr, ab, li, lu	+	17.0	112	1	462 (10)	— ^a		PD	—	1	
6	ab, lu, li, hi	+	No	168	4	197 (10)	318 (10)	2 li	PD	—	5	
7	li, lu	+	13.4	237	4	93 (7)	232 (7)		PD	su	4	
8	bo, lu, li, mu	NA	No ^b	112	3	385 (10)	— ^a		PD	—	2	
9	lr, ab, li, lu, hi	NA	No	112	2	209 (10)	266 (10)		PD	RIT, th	31	
10	lr, li, hi, sc	NA	No ^c	168	4	501 (10)	480 (10)		PD ^d	RT, RCT	6	

B, bevacizumab; C, capecitabine. Mets, metastases. Site of tumour manifestation: lr, local recurrence; li, liver; lu, lung; bo, bone; ab, abdominal; mu, muscular lesion; ax, axillar lesion; sc, supraclavicular lesion; hi, hilar lesion. NA, not available; +, positive VEGF staining. PD, progressive disease. su, sunitinib; vac, vaccination with survivin peptide; RIT, radioiodine therapy with iodometomidate; th, thalidomide; RT, radiotherapy; RCT, rosigitazone, celecoxib and trofosphamide.

^aPatient died before first control staging.

^bConcomitant RU486.

^cConcomitant metyrapone.

^dDespite stable target lesions the need for an emergency radiation therapy due to superior vena cava syndrome led to the diagnosis of PD.

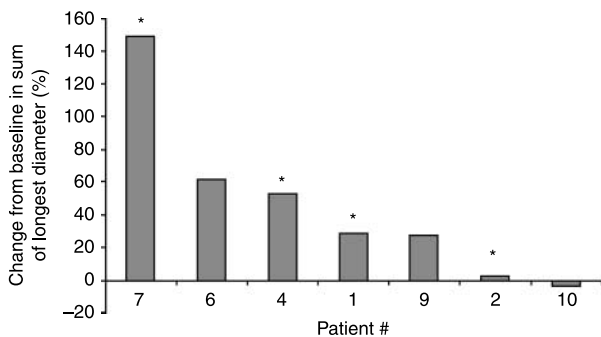


Figure 1 Maximal change (in per cent) from baseline in the sum of the longest diameter of predefined target lesion at the time of first staging during treatment with bevacizumab plus capecitabine in seven evaluable patients with advanced ACC. CT scans have been reviewed centrally by an independent radiologist. Each bar represents one patient. *Indicates patients with new detected metastases. Patient no. 10 developed superior vena cava syndrome and was, therefore, assessed as progressive disease.

no episode of hypertension was documented. Regarding the non-specific adverse events like nausea, vomiting or fatigue, we cannot exclude that mitotane has contributed to some of the negative effects. However, since only newly developed events were registered, it is not likely that mitotane is responsible for many of these events (Table 3).

Discussion

In our patient series, we found no evidence that the combination of bevacizumab and capecitabine is of benefit as salvage therapy for very advanced ACC. The disease was progressing in all patients with a median time to progression of only 59 days.

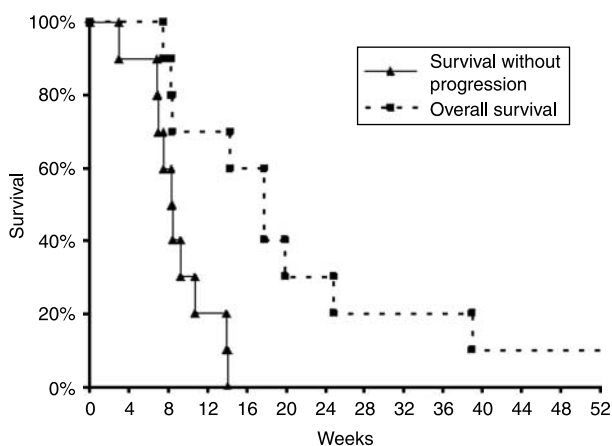


Figure 2 Survival without progression and overall survival in ten ACC patients treated with bevacizumab and capecitabine. One patient died outside the pictured timeline 31 months after starting bevacizumab and capecitabine.

Table 3 Adverse events in ten patients with advanced adrenocortical carcinoma (ACC)^a.

Event	Grade I	Grade II	Grade III	Grade IV
Fatigue	1	2	–	–
Nausea/vomiting	3	–	–	–
Fever	1	–	–	–
Leucopenia	2	–	–	–
Anaemia	1	1	–	–
Paraesthesia	–	1	–	–
Elevated serum creatinine	2	1	–	–
Hand-foot skin reaction	–	2 ^b	1 ^c	–
Rash/desquamation	–	1	–	–
Sweating	1	1	–	–
Oedema	1	1	–	–
Burning mucosa	1	–	–	–
Haematuria	–	1	–	–

^aNewly developed during the treatment with bevacizumab and capecitabine (according to NCI-CTG criteria (version 3.0)).

^bIn patient no. 1, therapy was stopped 14 days after starting bevacizumab and capecitabine.

^cPatient no. 4 suffered from hand-foot, skin reaction grade III, and therapy was therefore, in consideration of radiological proven tumour progression, stopped 21 days after starting bevacizumab and capecitabine.

Furthermore, all but one patient died within 9 months after initiation of bevacizumab and capecitabine. Clearly, our patient sample represented a negative selection due to advanced disease stage and several prior systemic treatment regimens. However, the complete lack of response to bevacizumab and capecitabine indicates a very limited potential in patients suffering from advanced ACC.

These disappointing results raise several questions: i) does this study indicate that both bevacizumab and capecitabine are not beneficial in patients with ACC at all? ii) was the relatively low dosage of bevacizumab and capecitabine responsible for the missing effectiveness? iii) does the combination of both drugs have even negative impact on the effects of the individual drugs? iv) would it be more effective to use this combination of drugs in patients not as heavily pretreated as our cohort? Although we cannot answer these questions with certainty, we caution against the assumption that both bevacizumab and capecitabine have in general no effect in patients with ACC. There are several explanations, why the treatment regimen failed: compared to former studies in other tumour entities, the dosage was reduced as a concession to the heavy cytotoxic pretreatment of the patients. Thus, we chose a dosage of 5 mg/kg body weight for bevacizumab every 3 weeks in contrast to 5 mg/kg body weight every 2 weeks used in colorectal cancer added on to the fluorouracil-based chemotherapy (21). In other tumour entities, even higher dosages of 10 mg/kg body weight every 2 weeks are used, and superiority in progression-free survival compared to 3 mg/kg body weight has been shown (24). However, in a compassionate use setting in

heavily pretreated patients with progressive malignancy, we aimed at avoiding toxicity. Furthermore, our dosage of 950 mg/m² capecitabine twice daily remained below the standard recommendation of 1250 mg/m² twice daily in breast, colorectal or gastric cancer. Capecitabine is absorbed through the intestine and converted to 5'-deoxy-S-fluorouridine (5'-DFUR) and finally, thymidine phosphorylase (TP) converts 5'-DFUR to the active drug 5-FU. This occurs in both tumour and normal tissues; however, TP is found at higher concentrations in most tumour tissue compared with normal healthy tissue. TP expression has been shown to be associated with response to capecitabine in lung cancer (30) and colorectal cancer (31). Although TP activity was detected in ACC (19), we cannot exclude that in advanced disease, dedifferentiation leads to downregulation of TP activity hampering the required conversion into the active compound. Furthermore, with this case series, we cannot verify whether the lack of benefit might be related to pharmacokinetic interactions, but there is no evidence that both drugs interfere with each other. In contrast, data from metastatic colorectal cancer showed a positive effect on progression-free survival by combining bevacizumab and XELOX (capecitabine plus oxaliplatin) versus XELOX alone (27). In addition, it is important to emphasize that our patients had a median of four affected organ sites and had received a median of 4 (range 3–5) prior systemic treatments. These pretreatment regimens might have induced a selection of aggressive dedifferentiated tumour cells not responding to any drugs.

The observed adverse events in our cohort were mainly mild and anticipated. In two patients, treatment had to be stopped due to hand-foot syndrome. This is a common adverse effect of capecitabine, and the percentage of treatment interruptions was not exceptionally high in comparison to other studies. In a meta-analysis of 13 studies, 47% of the patients developed hand-foot syndrome (32).

Our study confirms the disappointing results of salvage therapies in ACC reported in other studies (29, 33, 34). It further demonstrates that the natural course of ACC is progressive and that spontaneous tumour regressions as described for other tumour entities, e.g. melanoma (35), hepatocellular carcinoma (36) or colorectal cancer (37) are extremely unlikely.

We are well aware of the limitations of our study. One of the main drawbacks of our study is that it is not a formal phase II trial. However, until recently, pharmaceutical companies showed no interest to support clinical trials in such a rare disease, and also public funding resources for salvage concepts in rare tumour entities are virtually non-existent. However, our case series has several advantages in comparison with previous case series: the treatment protocol and the evaluation of response were performed prospectively in a standardized manner, and all images were reviewed

centralized by an independent radiologist according to RECIST criteria. In addition, the number of reported patients might seem to be low. However, ten patients with clearly progressive disease are probably enough to conclude that bevacizumab plus capecitabine is not effective in ACC refractory to several cytotoxic drug regimes. In this context, it seemed not justifiable to enlarge our series.

In conclusion, we found no benefit of bevacizumab plus capecitabine in pretreated patients with advanced ACC. Therefore, this regimen cannot be recommended as salvage therapy in this disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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