

Treatment of Advanced Adrenocortical Carcinoma with Erlotinib plus Gemcitabine

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Context: Adrenocortical carcinoma (ACC) is a rare malignancy with poor prognosis. In advanced disease, mitotane given as monotherapy or combined either with etoposide, doxorubicin, and cisplatin or with streptozotocin is the recommended first-line therapy. However, many patients have progressive disease despite treatment with these regimens.

Objective: Our objective was to evaluate the efficacy of the epidermal growth factor receptor inhibitor erlotinib plus gemcitabine as salvage therapy in ACC patients with very advanced ACC.

Design/Setting: The study consisted of case series collected from different centers (primary care and referral centers) in Germany in 2006–2007.

Patients and Intervention: Patients registered with the German ACC Registry with progressive ACC after two to four previous systemic therapies were offered treatment with erlotinib and gemcitabine. Oral erlotinib (100 mg/d) was administered on a daily basis and gemcitabine (800 mg/m²) iv every 14 d.

Main Outcome Measure: We evaluated tumor response according to response evaluation criteria in solid tumors (RECIST) criteria after 12 wk of treatment.

Results: Ten patients have been treated with erlotinib and gemcitabine. Only one in 10 patients experienced a minor response (progression-free survival 8 months), whereas eight patients had progressive disease at the first staging. One patient had to stop therapy after the first administration of gemcitabine due to cerebral seizure. Nine of 10 patients had died after a median of 5.5 months after treatment initiation. In addition to the seizure, one patient experienced severe pneumonia (grade III), and in one, gemcitabine administration had been delayed due to prolonged neutropenia. All other adverse events were mild (grade I–II).

Conclusions: Salvage chemotherapy using erlotinib plus gemcitabine has very limited to no activity in patients with very advanced ACC. (*J Clin Endocrinol Metab* 93: 2057–2062, 2008)

Adrenocortical carcinoma (ACC) is a rare disease with poor prognosis (1–3). In recent series, the overall 5-yr survival ranged from 23–60% (4–7). Survival is clearly stage dependent, and in advanced disease (stage IV), median survival ranges from 6–20 months (stage IV) only (3, 6, 8, 9), indicating the need for new treatment options. The adrenolytic agent mitotane is widely

employed in the medical treatment of advanced ACC and leads to control of hormone excess in the majority of patients. However, objective tumor regression occurs in only about 25% of cases (10).

Due to the rarity of the disease, cytotoxic chemotherapy was first reported in single cases or small case series, and until re-

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Abbreviations: ACC, Adrenocortical carcinoma; CT, computed tomography; EGFR, epidermal growth factor receptor.

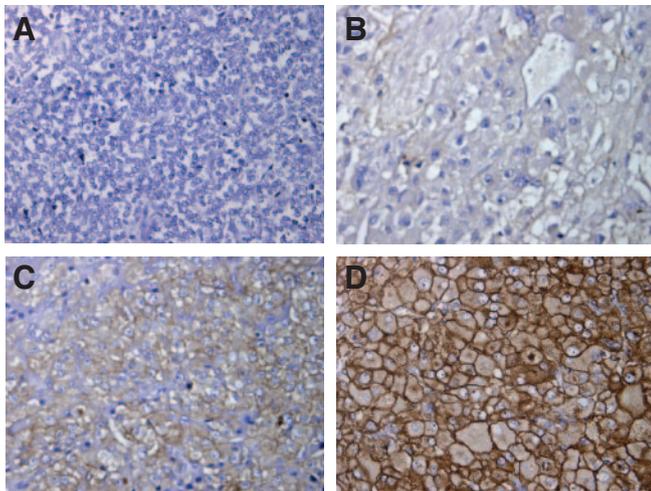


FIG. 1. Expression of EGFR by immunohistochemistry in ACC. A, No (score 0); B, weak (score 1); C, average (score 2); D, strong membrane staining (score 3).

cently, no more than nine phase II studies for first-line treatment with cytotoxic drugs have included 10 or more patients (10–19). There is even less experience with second-line treatments with only two studies including a total of 23 patients (20, 21). Cisplatin has emerged as the most widely used drug either alone or in combination with other agents (for review see Refs. 22 and 23). Based on this still limited experience with cytotoxic chemotherapy, the International Consensus Conference on Adrenal Cancer held in Ann Arbor, Michigan, in 2003 recommended the combination of mitotane either with etoposide, doxorubicin, plus cisplatin (13) or with streptozotocin (15) as the two best choices for treatment of advanced ACC (2). These two treatment options are currently compared in the first-ever randomized trial in this disease (FIRM ACT trial, www.firm-at.org). Up to now, more than 155 patients have already been enrolled, but results will not be available before 2011 after inclusion of 300 patients.

The initiation of the FIRM-ACT trial has led to a profound change in the care of patients with ACC because now an increasing number of patients with ACC are seen in the participating specialized centers. 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 GANIMED (German Adrenal Network Improving Treatment and Medical Education) 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 very advanced 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.

At the consensus conference in Ann Arbor, gemcitabine, a nucleoside analog with limited toxicity, was judged as one of several potential options for second- and third-line therapies, although its activity in ACC has never been tested in a clinical trial (2).

The epidermal growth factor receptor (EGFR) plays a pivotal role in tumorigenesis (24), with many human cancers overexpressing EGFR (25). In recent years, it has become an important target for therapies in different tumor entities. For instance, the EGFR tyrosine kinase inhibitor erlotinib led to improved survival in non-small-cell lung cancer patients failing standard first- or second-line therapy (26). In advanced pancreatic cancer, the combination of erlotinib and gemcitabine increased significantly the 1-yr survival in comparison with the standard gemcitabine monotherapy; however, the objective response rates were not significantly different (27).

In adrenal tumors, the EGFR system has been studied in a small series, and the expression of EGFR has been found to be present in the vast majority of ACCs (28–30). This finding was recently confirmed by us, when we analyzed 166 ACC samples by immunohistochemistry. In addition, preclinical data suggest that inhibition of the EGFR signaling pathway lead to a significant inhibition of proliferation in the ACC cell line NCI-H295 (31).

Therefore, we hypothesized that erlotinib in combination with gemcitabine might be of benefit also in patients with ACC. Here we report on the treatment of erlotinib and gemcitabine on

TABLE 1. Patients' characteristics and previous therapies

Patient	Sex	Age (yr)	Hormonal activity	Time from diagnosis of ACC to start of EG (months)	Time from diagnosis of metastasis to start of EG (months)	No. of previous surgeries	Previous systemic therapies	Previous RT/RFA
1	Male	38	A	16	9	4	M, Sz-M (2), EDP-M (5)	
2	Male	46	N	17	17	1	M, EDP-M (8), Sz-M (2)	
3	Male	45	N	16	16	1	M, Th, EDP-M (4), Sz-M (4)	RT skull
4	Male	45	N	19	19	2	M, Sz-M (4), EDP-M (2)	
5	Male	50	N	14	10	1	M, EDP-M (4), Sz-M (2)	
6	Female	30	C	19	19	2	M, EDP-M (6), Sz-M (2)	RFA liver
7	Female	26	N	5	5	1	M, Sz-M (2), EDP-M (2)	
8	Male	62	N	17	6	1	M, EDP-M (4), Sz-M (2)	
9	Male	66	N	72	33	4	M, EC (21), Sz-M (2)	
10	Female	72	A	20	20	1	M, Sz-M (6), EDP-M (12)	

The duration of previous chemotherapies is given in months in *parentheses*; diagnosis of progressive disease resulted in a switch of the therapy. A, Androgen; C, cortisol; EC, etoposide, carboplatin; EDP-M, etoposide, doxorubicin, cisplatin, mitotane; EG, erlotinib plus gemcitabine; M, mitotane monotherapy; N, hormonally inactive or with no initial hormonal work-up; RFA, radiofrequency thermal ablation; RT, radiotherapy; Sz-M, streptozotocin and mitotane; Th, thalidomide.

TABLE 2. Disease status and results of evaluation

Patient	Sites of tumor manifestation	EGFR expression score	Concomitant mitotane	Cumulative E dose (g)	Cycles of G	Sum (mm) of the longest diameter (target lesions)		No. of new metastases 12 wk after start EG	Overall response	Survival since start of EG (months)
						Before EG	12 wk after start EG			
1	Local recurrence, lung, abdomen, axilla	3	No	7.7	6	87	129	>15 (lung)	PD	13
2	Local recurrence, lung, hilar lesion, abdomen, liver	3	Yes	8.4	6	226	326	2 (lung)	PD	6
3	Local recurrence, liver, lung, bone, abdomen	3	Yes	6.3	4	223	378	>4 (lung, liver)	PD	4
4	abdomen, lung, muscular		Yes	0.1	1	237	NA ^a	NA	PD	5
5	Local recurrence, abdomen, liver, lung	2	Yes	7.0	5	315	464	>10 (lung)	PD	4
6	Local recurrence, liver, lung, abdomen	3	Yes	6.3	4	230	514 ^b	>20 (lung, liver)	PD	7
7	Local recurrence, liver, lung, abdomen	3	Yes	6.0	6	400	612 ^c		PD	3
8	Liver, lung	3	Yes	16.8	11	42	82	2 (liver)	PD	12
9	Local recurrence, liver	2	No	6.3	4	159	190	2 (liver, abdomen)	PD	6
10	Lung, liver, abdomen, hilar lesion	1	Yes	24.5	13	105	88		SD	12 (alive)

E, Erlotinib; G, gemcitabine; PD, progressive disease; SD, stable disease.

^a EG determined after first administration of G, therefore not evaluable.

^b Follow-up examination performed by CT without contrast media.

^c Follow-up examination performed by ultrasound.

a compassionate-use basis in 10 patients with advanced ACC failing two to four other systemic therapies.

Patients and Methods

Patients

Between February 2006 and October 2006, 10 patients within the German ACC Registry fulfilled the following criteria: histologically proven ACC in an unresectable, locally advanced, recurrent, or metastatic stage after progression despite treatment with mitotane and two to four cytotoxic chemotherapies including one platin-based chemotherapy. All patients had radiologically measurable disease as defined by response evaluation criteria in solid tumors (RECIST) criteria (32), were aged over 18 yr, and were in acceptable clinical condition [Eastern Cooperative Oncology Group (ECOG) stage of 0–2] with adequate hematological, renal, and hepatic function. Exclusion criteria included previous exposure to EGFR-directed agents or gemcitabine, other malignancies within 5 yr, and active infection. All patients were informed of the experimental nature of the treatment and signed informed consent.

Treatment protocol

Erlotinib (Tarceva; Hoffmann-La Roche, Basel, Switzerland) was administered orally 100 mg/d in a continuous manner. Gemcitabine (Gemzar; Lilly, Bad Homburg, Germany) was given iv every 2 wk in a dosage of 800 mg/m² as an infusion over 30 min. In general, the therapy was carried out on an outpatient basis. Concomitant administration of mitotane was permitted.

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/glutamate oxaloacetate transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), alkaline phosphatase, total bilirubin, and albumin], and chest and abdominal computed tomography (CT) scans were performed. This evaluation was repeated every 12 wk, and tumor response was determined. All radiological images were reviewed by an independent radiologist. Response was assessed using the response evaluation criteria in solid tumors (RECIST) (32). 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).

Immunohistochemistry

Immunohistochemical detection of EGFR expression was performed on standard sections of paraffin-embedded tumor samples of nine patients using an indirect immunoperoxidase technique after high-temperature antigen retrieval in 0.01 mol/liter citrate buffer (pH 6.0) for 25 min. The primary antibody (NCL-LEGFR; Novocastra, Newcastle upon Tyne, UK), an IgG2a antibody against the external domain of the EGFR molecule, was used in a dilution of 1:20 and incubated for 60 min at 25 C. The secondary antibody coupled with peroxidase was obtained from Biotex (Neufahrn, Germany). The slides were incubated with the secondary antibody for 20 min and washed in PBS before diaminobenzidine as chromogen was applied. After washing in PBS and H₂O, the slides were counterstained in hematoxylin.

Staining intensity was determined semiquantitatively using a four-grade (0, 1+, 2+, 3+) system (Fig. 1).

TABLE 3. Adverse events

Event	Grade I	Grade II	Grade III	Grade IV
Skin rash	2	2	0	0
Fatigue	2	1	1	0
Infection	0	0	1	0
Nausea/vomiting	0	1	0	0
Cerebral seizure	0	0	1	0
Leukopenia	2	2	0	0
Anemia	7	1	0	0
Elevated liver enzymes	3	1	0	0
Paraesthesia	1	0	0	0
Elevated serum creatinine	1	0	0	0
Proteinuria	1	0	0	0

Adverse events were those newly developed during the treatment with erlotinib and gemcitabine (according to National Cancer Institute–Common Toxicity Criteria, version 3.0).

Results

Patient characteristics

From February 2006 to June 2007, 10 patients (seven males, three females) were treated with erlotinib and gemcitabine. Detailed patient's characteristics are given in Table 1. All patients were heavily pretreated including surgery, mitotane, and at least two cytotoxic chemotherapy regimens. In several patients, repeated surgery, radiation therapy, or radiofrequency thermal ablation had been performed. Eight patients had been enrolled within the FIRM-ACT trial and had received both etoposide, doxorubicin, and cisplatin plus mitotane and streptozotocin plus mitotane. In the two remaining patients, a platin- and etoposide-containing regime had been administered followed by streptozotocin plus mitotane.

All patients had significant tumor burden involving at least two different organ sites. Details are given in Table 2. Eight patients were maintained on mitotane during treatment with erlotinib and gemcitabine mainly to control hormone excess or because of previous treatment with good tolerance.

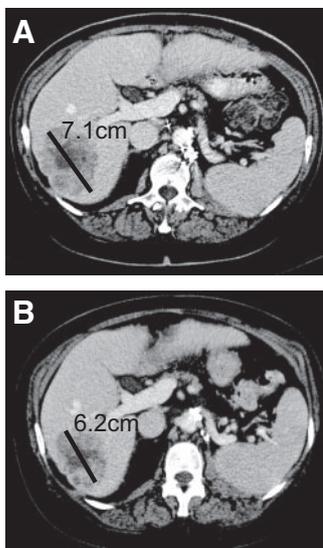


FIG. 2. CT scan of liver metastasis in patient 10 with advanced ACC before (A) and after (B) 12 wk of treatment with erlotinib (100 mg/d) and gemcitabine (six cycles) demonstrating a minor tumor response.

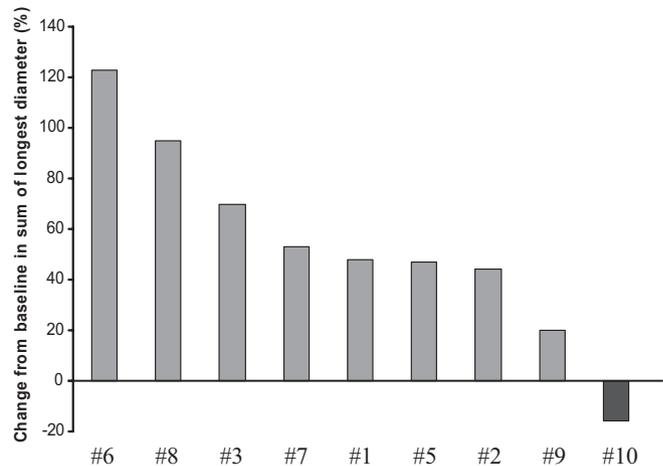


FIG. 3. Maximal change (in percent) from baseline in the sum of the longest diameter of target lesion after 12 wk of treatment with erlotinib and gemcitabine in nine patients with very advanced ACC. CT scans have been reviewed centrally by an independent radiologist. Each bar represents one patient.

In nine of 10 patients, EGFR expression in the tumor was evaluated, and EGFR protein was detectable in all investigated samples (Table 2). In six patient samples, a strong EGFR expression was detected, whereas in two tumors, the intensity of expression was average, and in one tumor weak.

Outcome

Only one of 10 patients (patient 10) experienced a minor tumor response (Fig. 2) leading to a progression-free survival of 8 months. In eight patients, progressive disease was detected at the time of the first evaluation after 12 wk (Table 2 and Fig. 3). In one patient, treatment was stopped after the administration of the first cycle of gemcitabine, because he experienced a cerebral seizure the day after the first administration. In the meantime, nine of 10 patients have died with a median survival of 5.5 months after starting erlotinib and gemcitabine. The patient with the minor response is still alive 12 months after initiation of erlotinib and gemcitabine.

Apart from the seizure, adverse events were mainly mild. In one patient, administration of gemcitabine had to be delayed twice due to neutropenia, and one patient developed a severe pneumonia. In all other patients, therapy was well tolerated. Erlotinib induced rash in four patients, and four patients reported on fatigue, but dose modification was not required in any patient. Table 3 summarizes the adverse events during the treatment period.

Discussion

Our patient series provides evidence that the combination of erlotinib and gemcitabine is of very limited to no effectiveness in the control of progressive ACC in heavily pretreated patients. Only one of 10 patients had a minor response and a progression-free survival of 32 wk, whereas no tumor response was seen in the other patients. Even though patient 10 had the lowest expression of EGFR (Table 2), she had the best response among all patients.

Of note, the patients with the highest expression of EGFR had no response, indicating a lack of correlation of target expression and efficacy of treatment. Although our patient sample clearly represents a negative selection due to the many preceding treatment modalities, our findings do not indicate that this combination holds relevant therapeutic potential in advanced ACC.

Our study has several limitations. Most important, it is not a formal phase II trial but represents a case series given one of different available salvage therapy options as a compassionate treatment. However, until very recently, pharmaceutical companies showed little interest in supporting clinical trials in ACC. This fact and the rarity of the disease made a formal phase II trial investigating salvage treatments virtually unfeasible. All patients in our series knew the experimental nature of the therapy and gave their written informed consent. Moreover, both the treatment protocol and the evaluation were performed prospectively in a standardized manner with centralized review of images by an independent radiologist.

Our findings of poor to no clinical response to erlotinib and gemcitabine treatment differed from several but not all preclinical and clinical studies with erlotinib in other tumor entities. In mice bearing human non-small-cell lung cancer xenografts, co-administration of erlotinib with (cisplatin or) gemcitabine produced additive or synergistic antitumor activity (33). The mechanisms by which erlotinib may achieve antitumor activity when added to chemotherapy remain to be further elucidated. In patients with advanced pancreatic cancer, erlotinib plus gemcitabine prolonged survival statistically significantly compared with gemcitabine alone; however, the objective response rates were not significantly different, and the magnitude of benefit was only 14 d (27). Erlotinib plus gemcitabine and cisplatin failed to improve outcome in patients with non-small-cell lung cancer (34). The reasons for the lack of benefit from erlotinib plus chemotherapy are unknown but are not related to the pharmacokinetics of gemcitabine, because previous results indicated that erlotinib had no effect on plasma levels of gemcitabine or cisplatin, and vice versa (34). Thus, a negative pharmacokinetic interaction between erlotinib and chemotherapy is unlikely. Therefore, we can only speculate why erlotinib and gemcitabine were inefficient in our patient cohort. Several factors may play a role. 1) Both drugs might be not suitable for the treatment of ACC. 2) The interaction of these drugs in ACC might be not ideal. Erlotinib acts mainly cytostatic and gemcitabine cytotoxic. The antiproliferative effects of erlotinib, arising from cell-cycle arrest (35), may render tumor cells less sensitive to cytotoxic agents. 3) The used dosage might be too low. However, this is unlikely for erlotinib, because 100 mg/d is the standard dose and was effective in other tumor entities (27). In contrast, gemcitabine is sometimes used in higher dosages (1000–1250 mg/m²) and/or shorter time intervals (weekly). Because all our patients were heavily pretreated with cytotoxic drugs, for safety reasons, we used only 800 mg/m² gemcitabine every 2 wk. This dose has been successfully used with acceptable toxicity in metastatic soft-tissue sarcomas in combination with vinorelbine (36) but may be too low for ACC. 4) In addition, it is important to emphasize that our patients had very advanced ACC and had received mitotane treatment and at least two cytotoxic chemotherapy regimens

before treatment initiation. However, we cannot exclude that erlotinib or gemcitabine may have more effects on ACC when these drugs are used in an earlier stage of disease or in combination with other drugs.

The majority of our patients had significant increase in tumor burden (Table 2 and Fig. 3), indicating the very aggressive nature of advanced ACC. This is in agreement with two studies investigating cytotoxic drugs as salvage therapy (20, 21).

In conclusion, our case series suggests that erlotinib plus gemcitabine has very limited to no activity as salvage therapy in patients with advanced ACC.

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