RESEARCH

Pharmacokinetic interaction between mitotane and etoposide in adrenal carcinoma: a pilot study

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Abstract

Background: The combination of mitotane and platinum-etoposide chemotherapy is a front-line treatment in metastatic adrenocortical carcinoma (ACC), although this regimen shows limited efficacy. Pharmacokinetic drug–drug interaction between mitotane, a strong CYP3A4 inducer, and etoposide, which is a substrate of CYP3A4, may contribute to chemoresistance. The aim of this pilot study was to assess the pharmacokinetic interaction between mitotane and etoposide in ACC patients.
Methods: Five consecutive ACC patients treated with platinum etoposide (120–150 mg/m^2 day 1–2–3 at cycle 1), with or without concomitant mitotane, were included. In the absence of limiting toxicity, a dose escalation of etoposide was proposed since cycle 2. Plasma etoposide concentrations were measured using liquid chromatography at 0, 4 and 24 h after each infusion. Clearance and area under the curve (AUC) of etoposide were determined at each cycle.
Results: Patients received two to six chemotherapy cycles, in association with mitotane (*N*=4) or after mitotane discontinuation (*N*=1). Etoposide clearance was two-fold higher with concomitant mitotane (4.95 L/h) than after mitotane discontinuation (2.53 L/h, *P*=0.014), and 2.5-fold higher than that in reference population not treated with mitotane (1.81 L/h). Etoposide dose escalation was performed in four patients under mitotane, resulting in two minor tumor responses and one severe toxicity (febrile aplasia) at dose of 300 mg/m^2/day. Tumor response was associated with higher etoposide AUC (267.3 vs 188.8 mg.h/L, *P*=0.04).
Conclusion: A drug–drug interaction between mitotane and etoposide may contribute to the low efficacy of platinum-etoposide chemotherapy. This pilot study suggests further a potential benefit of increasing etoposide dose in ACC patients receiving mitotane.

Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy (1 per million each year) with a poor prognosis (1). Even after complete surgery, up to 70% of patients will develop recurrence (1). Medical treatments show limited efficacy and the extreme rarity of the disease hampers the development of new drugs (2). The combination of mitotane and etoposide/doxorubicin/cisplatin (EDP) is now the standard treatment in advanced ACC (3). However, overall response rate (23%) and progression-free survival (5 months) remain disappointing. Furthermore, lower rates of severe hematological toxicities are observed with EDP-mitotane regimen than with platinum-etoposide in small-cell lung cancer (SCLC) patients (11 vs 53% of grade 3–4 neutropenia) (4). Since neutropenia is commonly associated with etoposide AUC (5), this may indicate a lower plasma etoposide exposure in ACC patients treated with mitotane. Indeed, mitotane is a strong inducer of cytochrome P450 3A4 (CYP3A4) and ATP-binding cassette (ABC) multidrug transporters (6), while etoposide is a substrate of these proteins (7, 8). We hypothesized that chemoresistance in ACC could partly result from an infra-therapeutic plasma exposure to etoposide, due to concomitant administration of mitotane. The aim of this pilot study was to assess the pharmacokinetic interaction between mitotane and etoposide in ACC patients treated with mitotane and platinum-etoposide chemotherapy.

Patients and methods

Patients

This pilot study was conducted from December 2016 to October 2017 in the national referral center for adrenal diseases and the oncology department at Cochin Hospital, Paris. Consecutive patients with metastatic ACC receiving platinum-etoposide chemotherapy were included. Mitotane was pursued or stopped before chemotherapy initiation at the discretion of physician. The adjustment of mitotane daily dosing for each patient (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article) was based on the trough plasma level, which was to be within the recommended range of 14–20 mg/L (9). Etoposide was administrated intravenously on days 1, 2 and 3 of each 3-week cycle, starting at a dose of 120–150 mg/m²/day at cycle 1. In the absence of limiting toxicity, a dose escalation of etoposide could be proposed from cycle 2. Efficacy was assessed by CT scan every three

cycles. Objective responses that did not meet the Response Evaluation Criteria In Solid Tumors (RECIST) criteria were classified as 'minor responses'. Toxicity was assessed at each cycle according to the Common Terminology Criteria for Adverse Events, and weekly complete blood count was performed to monitor hematological toxicity.

Consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used. The study was approved by the local institutional review board ('Comité Local d'Ethique en Cancérologie') according to the Declaration of Helsinki.

Pharmacologic assessments

Mitotane plasma concentration was determined at each start of 3-week cycle by liquid chromatography, as previously described (10). Etoposide plasma concentrations were measured at the end, 4 and 24 h after each perfusion. Clearance and area under the curve (AUC) of etoposide were determined at each cycle with a Bayesian approach using a population pharmacokinetic method (NONMEM program, version 7, level 2.0) and a dataset of rich pharmacokinetic data from 50 patients, as previously described (11).

Statistics

Descriptive statistics used median for quantitative variables. Comparisons between groups were assessed with Mann–Whitney test, and correlations with Spearman coefficient. All P values were two-sided, and the level of significance was set at $P < 0.05$. Calculations were performed using R statistical software v3.4.4 (R Stats Package).

Results

Patients

Five consecutive patients with metastatic ACC were included after progression under mitotane monotherapy (Table 1). Median age was 40 years. All tumors were cortisol secreting and were rapidly progressive with a median time since diagnosis of 5 months. All patients presented normal hepatic and renal function before and throughout cycles of platinum-etoposide chemotherapy.

A median of four cycles (range 2 to 6) of platinum-etoposide chemotherapy were administered, in association

Table 1 Patients' characteristics.

Patient	Age (years)	Gender	Time since diagnosis (months)	Steroid secretion	ENSAT stage at diagnosis	Metastatic sites	Trough mitotane level[a] (mg/L)	Chemotherapy regimen	Number of cycles	Etoposide dosage (mg/m²)	Best response	Grade 3-4 toxicities	Causes for treatment discontinuation
1	48	Female	19	Cortisol	III	Liver	10.3–13	Carboplatin etoposide	2	150–180	Progressive disease	None	Progressive disease
2	18	Female	2	Cortisol Androgens	IV	Liver Lung	0.9–2.2 (stopped before chemotherapy)	Carboplatin etoposide	6	120	Stable disease	None	End of treatment
3	28	Male	2	Cortisol Androgens	IV	Liver Lung	6.8–23.6	Carboplatin etoposide	6	180–300	Minor response (RECIST stable disease)	None	End of treatment
4	40	Female	5	Cortisol Androgens	IV	Lymph nodes Lung Liver Bone	16.1–16.1	Cisplatin etoposide	2	150–200	Progressive disease	None	Progressive disease
5	50	Female	10	Cortisol Androgens	II	Adrenal lodge Peritoneal carcinomatosis	13.8–22.6	Cisplatin etoposide	4	150–300	Minor response (RECIST stable disease)	Febrile aplasia	Toxicity

[a]Range of trough mitotane level during the whole etoposide therapy. ENSAT, European Network for the Study of Adrenal Tumors.

with mitotane for four patients or after mitotane discontinuation for one patient.

Etoposide pharmacokinetics reveals drug–drug interaction between etoposide and mitotane

Overall, 163 drug plasma concentrations were available for analysis, 20 for mitotane and 143 for etoposide. Median mitotane plasma concentration was 13.8 mg/L (0.9–28.7 mg/L) over the whole study period.

Inter-individual and intra-individual variability in etoposide clearance were 45.4 and 9.6%, respectively. Etoposide clearance was 2-fold higher in patients concomitantly treated with mitotane (median 4.95 L/h (2.67–6.20)) than after mitotane discontinuation (median 2.53 L/h (2.02–2.78), $P = 0.014$, Fig. 1), and 2.5-fold higher than that reported in a reference population pharmacokinetic study (mean ± s.d.: 1.81 ± 0.58 and 1.92 ± 0.52 L/h) (11, 12). Etoposide clearance was not statistically correlated with mitotane concentration ($r = 0.37$, $P = 0.14$, Fig. 1).

Efficacy and safety of etoposide dose escalation

Etoposide dose escalation was performed in the four patients treated with mitotane. Two minor tumor responses, one stable disease and two progressive diseases were observed (Table 1). Etoposide AUC were higher in
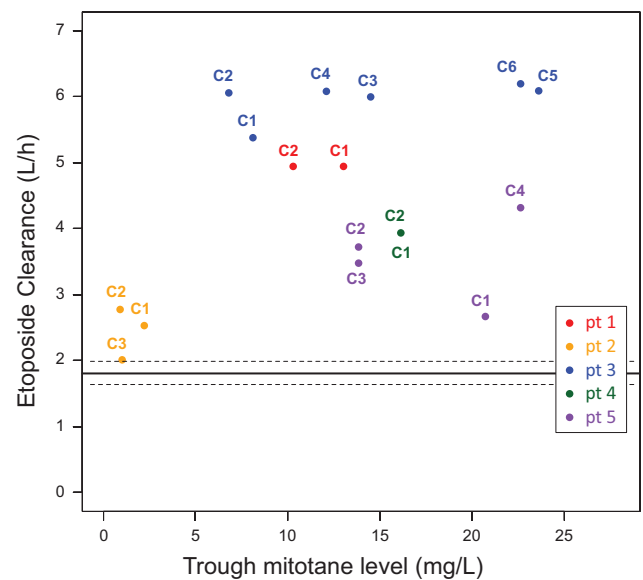
Figure 1
Relation between trough mitotane level and etoposide pharmacokinetics. Horizontal lines represent mean and 95% CI interval of etoposide clearance in a reference population not treated with mitotane (11).
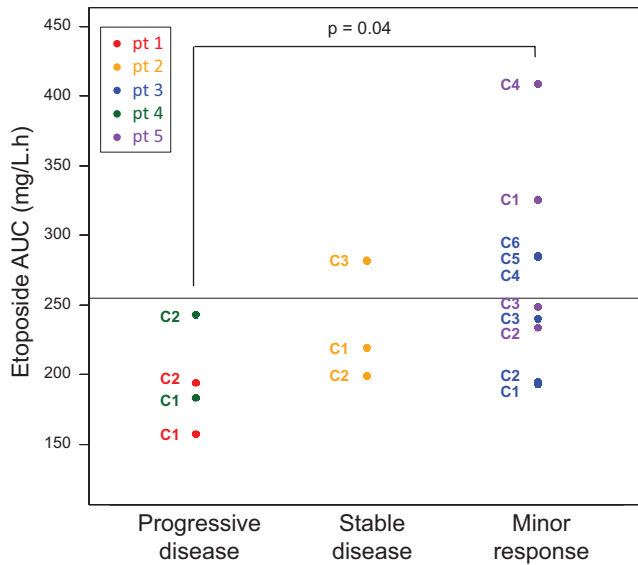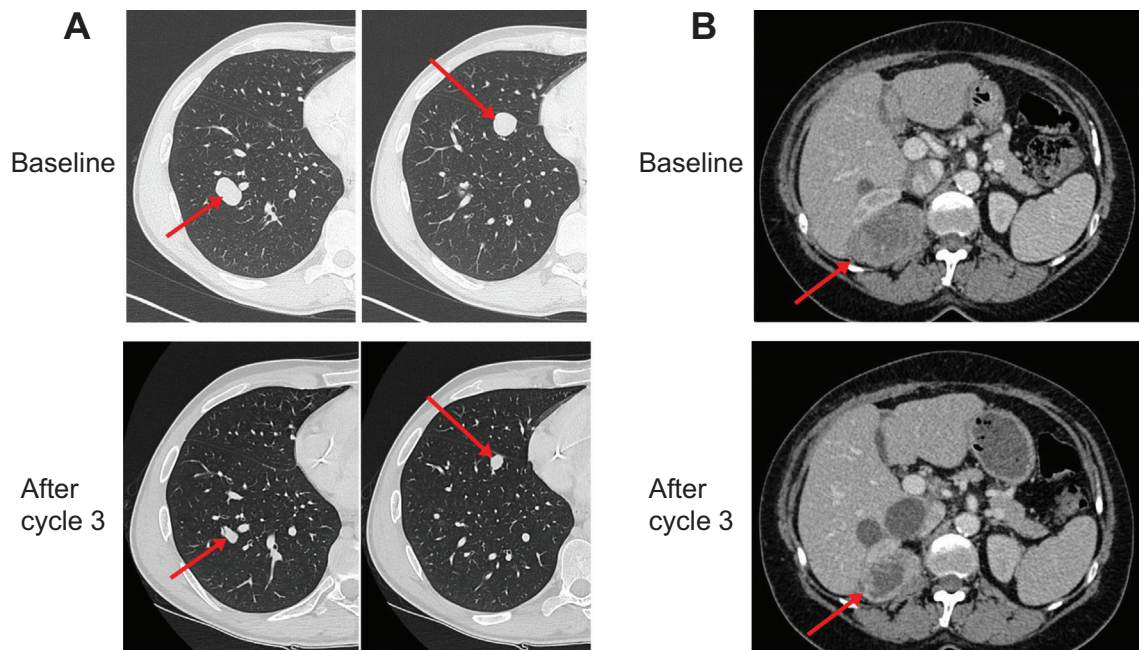
Figure 2
Relation between etoposide exposure and best response to platinum-etoposide chemotherapy. AUC, area under the curve. Horizontal line represents threshold AUC associated with survival in small-cell lung cancer (18).

patients with tumor response (median 267.3 mg.h/L (193.1–408.8)) than in patients with progressive disease (median 188.8 mg.h/L (157.6–243.0), $P = 0.04$, Fig. 2). The two minor responses (Fig. 3A and B) were obtained at etoposide dose of 300 mg/m^2. One severe adverse

event (febrile aplasia) occurred on 1/20 chemotherapy cycles (5%) at etoposide dose of 300 mg/m^2 with a rapid favorable outcome.

Discussion

The presents study demonstrates for the first time a pharmacokinetic drug–drug interaction between mitotane and etoposide in the treatment of advanced ACC. Etoposide clearance was 2.5-fold higher in patients concomitantly treated with mitotane than in reference population not treated with mitotane (11, 12). Interestingly, Baker *et al.* also reported a 2.5-fold higher clearance of teniposide – which is a semisynthetic etoposide-like derivative of podophyllotoxin (13) – when patients received concomitant phenobarbital – which is a strong inducer of CYP3A4 and P-glycoprotein (P-gp) (14). Mitotane could induce both CYP3A4 and ABC transporters, notably breast resistance cancer protein (BCRP) and P-gp (6, 15). These two important efflux proteins are known to contribute to the biliary and digestive excretion of etoposide (16, 17). Thus, mitotane could increase both the metabolic clearance and excretion of etoposide, resulting in infra-therapeutic drug plasma exposure.

Figure 3
Tumor evolution in patients presenting with minor responses after platinum-etoposide chemotherapy. (A) Decrease of lung metastases (red arrows) in patient 3. (B) Decrease of adrenal lodge recurrence (red arrow) in patient 5.

In our study, the two patients with progressive disease were concomitantly treated with mitotane and exhibited etoposide AUC ranging from 157.6 to 243.0 mg.h/L. In SCLC patients, etoposide AUC below 254.8 mg.h/L were significantly associated with shorter survival ([18], [19]). Although target AUC for efficacy may vary from one tumor type to another, this result suggests an infra-therapeutic etoposide AUC in our patients experiencing progressive disease. Finally, BRCP and P-gp are highly expressed in ACC in comparison to other tumor types ([20]). Mitotane could even increase the expression of these proteins in tumor cells, thus limiting the intra-tumor diffusion of etoposide, and thereby conferring chemotherapy resistance.

Overall, the pharmacokinetic interaction with mitotane in ACC patients could partly explain the limited efficacy of antiangiogenic kinase inhibitors ([21], [22], [23]), which are also substrates of CYP3A4 and ABC transporters. Indeed, in a phase II trial, efficacy and toxicity of sunitinib (0% of response and 26% of grade 3–4 adverse events) were lower than expected in ACC patients. Most of these patients received mitotane and were underexposed to sunitinib compared to the target plasma therapeutic level ([21]). Pharmacokinetic assessment should be included in future clinical trials to address the potential effect of mitotane on plasma exposure to co-administered antitumor therapy.

Optimizing the combination of etoposide with mitotane is a therapeutic challenge since the rarity of ACC hampers the development of new drugs. Given that the plasma elimination half-life of mitotane is up to 5 months ([24]), the discontinuation of mitotane just before etoposide initiation would not be sufficient to prevent the pharmacokinetic interaction. Up to several months would be necessary for a complete disappearance of its inductor effect, which is unthinkable for such an aggressive tumor. The present study paves the way for a dose escalation of etoposide. To date, a pharmacokinetically guided dosing for etoposide in ACC patients does not seem feasible for two reasons: first, the lack of target therapeutic AUC in this population; second, plasma drug monitoring for etoposide is not routinely available. Finally, in our study, there was no linear relation between mitotane trough level and etoposide clearance, and the inter-individual variability was quite high (45.4%). Genetic polymorphisms in drug-metabolizing enzymes ([25]), and/or pharmacokinetic durg–drug interaction with concomitant medications may partly explain this variability. For instance, patients 4 and 5 received respectively ketoconazole and diltiazem, which are known CYP3A4 inhibitors. These two patients exhibited a lower etoposide clearance (3.92 and 3.72 L/h respectively) than patients 1 and 3 (4.95 and 6 L/h respectively), while mitotane plasma levels were very close in these four patients (13–16.1 mg/L, Fig. 1). Therefore, it would not be possible to predict individually the adequate etoposide dosage from the mitotane trough level.

Kukec *et al.* showed that high plasma etoposide exposure was associated with both longer survival and increased severity of neutropenia in SCLC patients ([4]). Hence, the neutrophil blood count could be used as a surrogate of plasma drug exposure and therefore could be helpful to guide dosing optimization. Finally, in the present study, the mean daily dose of etoposide to achieve AUC above 254.8 mg.h/L was 270 mg/m^2 in patients receiving mitotane, and dose-limiting toxicity occurred only in one patient at dose of 300 mg/m^2. From this observation, a starting dose of etoposide of 150–200 mg/m^2 might be proposed to ACC patients receiving mitotane. Thereafter, a dose escalation of 50 mg/m^2 could be proposed at each cycle until the onset of grade 1–2 neutropenia or any grade 2 clinical toxicity. Of note, a close monitoring of etoposide-related adverse events should be recommended.

The main limitation of this study is the small sample size, which limits the statistical power and the generalization of the results. Especially, data on etoposide clearance after mitotane discontinuation derived from a single patient. Further studies with larger cohorts are needed to confirm these results and evaluate the potential benefit of etoposide dose escalation in this setting.

In conclusion, the drug–drug interaction between mitotane and etoposide may explain the limited efficacy of etoposide at standard dose in ACC patients. This pilot study suggests a potential benefit of etoposide dose escalation in ACC patients receiving mitotane.

Supplementary data

This is linked to the online version of the paper at https://doi.org/10.1530/EC-18-0428.

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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