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Prospective, Single-Center, Phase II Study to Standardize the Mitotane Dosing Regimen in Combination with Platinum-Based Chemotherapy in the First-Line Treatment for Adrenocortical Cancer

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Introduction. The combination of EDP (etoposide, doxorubicin, cisplatin) chemotherapy with mitotane represents the standard first-line therapy for adrenocortical carcinoma (ACC). Achieving therapeutic serum concentrations of mitotane has been associated with improved progression-free survival (PFS) and overall survival (OS) in several studies. However, mitotane dosing in most prior research has followed institution-specific protocols, underscoring the need for a validated and standardized dosing regimen.

Materials and Methods. A single-center, prospective, phase II study was conducted using a Simon's two-stage design. Eligible patients had locally advanced or metastatic ACC, ECOG performance status 0–1, and were naïve to mitotane. The primary endpoint was the rate of achieving therapeutic mitotane concentrations (14–20 μg/mL). The study aimed to increase this rate from a historical 50 to 70 % ($\beta = 0.2$; $\alpha = 0.05$). Secondary endpoints included objective response rate (ORR), disease control (DC) ≥ 6 months, PFS, OS, and safety. Mitotane was initiated at 2 g/day, with dose escalation by 0.5 g every 3–5 days to a maximum of 4 g/day, followed by titration based on serum drug levels. All patients concurrently received standard platinum-based chemotherapy (EDP or EP/EC).

Results. Forty-seven patients were enrolled (27 male, 57.4 %). All received platinum-based chemotherapy, 45 (95.8 %) with EDP, 2 with EP/EC. After a median follow-up of 12.4 months, therapeutic mitotane concentration was achieved in 72.3 % of patients (n = 34), with a median time to achievement of 4.3 months (95 % CI 3.3–5.3). The ORR was 29.7 %, and DC ≥ 6 months was 63.8 %. Median PFS was 8.4 months (95 % CI 4.2–12.6), and median OS was 24.6 months (95 % CI 9.9–44.6). The safety profile was consistent with prior reports.

Conclusion. The investigated mitotane dosing regimen facilitates rapid and safe attainment of therapeutic drug levels in the majority of patients and can be recommended for routine clinical practice.

Keywords: adrenocortical cancer; mitotane; EDP

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Introduction

Adrenocortical carcinoma (ACC) is an orphan malignancy with an incidence of approximately 0.8 cases per 1 million population per year. Due to its rarity, the majority of data on treatment outcomes for ACC are derived from retrospective studies or small prospective phase II trials [1]. Locally advanced (stage III) and metastatic ACC are identified at diagnosis in 18–26 and 21–46 % of cases, respectively, which often necessitates a comprehensive therapeutic approach combining surgery and systemic therapy [2–5].

The cornerstone of systemic treatment for ACC is mitotane, used both in the adjuvant setting and for metastatic disease. The efficacy of mitotane in the adjuvant setting is supported by a number of large retrospective studies: a recent meta-analysis demonstrated that its use reduces the risk of recurrence by 37 % [6–9].

The only prospective study of mitotane efficacy in the adjuvant setting was the ADIUVO trial. It evaluated the efficacy of mitotane compared to placebo in patients with low (stage I–II, Ki-67 < 10 %) and intermediate (stage III, Ki-67 < 10 %) risk of recurrence [10]. However, only 13 % of the enrolled patients belonged to the intermediate-risk group, limiting the generalizability of the results to this population [10]. A total of 91 patients were enrolled: 46 in the observation arm and 45 in the mitotane arm. The 5-year recurrence-free survival (RFS) was 75 % in the observation group and 79 % in the mitotane group; the difference was not statistically significant, and therefore the trial was considered negative. Consequently, current indications for adjuvant mitotane therapy are the presence of at least one unfavorable prognostic factor: Ki-67 > 10 %, stage III disease, or an R1 resection status [11, 12].

When mitotane is used as monotherapy in the first-line setting, the objective response rate (ORR) is 18 %, and disease control (DC) for ≥ 12 months is achieved in 22 % of patients. It is important to note that these data were obtained from a retrospective study in a cohort with a favorable prognosis, where 78 % of patients had a Ki-67 index < 20 % [13].

In addition to its antitumor effect, mitotane has an adrenolytic action, damaging intracellular enzymes involved in steroid synthesis, which leads to the suppression of adrenal steroidogenesis. Due to the inhibition of steroid synthesis, patients without hypercortisolism who are treated with mitotane require glucocorticoid replacement therapy. The reduction in circulating glucocorticoid levels is caused not only by the adrenolytic activity of mitotane but also by its ability to stimulate the hepatic clearance of steroids [14–17]. Consequently, most patients require a hydrocortisone replacement dose of 50–70 mg per day, which is approximately double the standard dose used for adrenal insufficiency of other etiologies [11]. Inadequate replacement therapy worsens the tolerability of mitotane.

A key feature of mitotane is its narrow therapeutic window (14–20 μg/mL): at lower concentrations its efficacy is reduced, while at higher concentrations the risk of central neurotoxicity increases [13, 18–20]. Achieving therapeutic mitotane concentrations is associated with improved progression-free survival (PFS) and overall survival (OS) [13, 21]. In most studies, including the prospective ADIUVO and FIRM-ACT trials, mitotane dosing protocols were defined by local practice. Therapeutic drug levels were achieved in only about half of the patients, even with high doses (> 6 g/day), which is attributed to the drug's poor water solubility, large volume of distribution, and variable bioavailability [22–24]. In the ADIUVO trial, the rate of achieving therapeutic mitotane concentrations in the adjuvant setting was only 59 %, whereas in expert centers this rate can reach 70 % [10, 13].

Thus, the standardization of mitotane dosing protocols and the assessment of their safety, as well as the rate of achieving therapeutic drug concentrations, remain clinically relevant challenges. This was precisely the primary objective of the present study. Secondary endpoints included the ORR, DC for ≥ 6 months, PFS, OS, and treatment safety.

Materials and Methods

Inclusion criteria

Histologically confirmed locally advanced inoperable or metastatic adrenocortical carcinoma (T4N0-1M0 or M1); age ≥ 18 years; ECOG performance status 0–2; no prior mitotane therapy. A history of platinum-based chemotherapy as adjuvant therapy was permitted, provided the recurrence-free interval after its completion was ≥ 12 months. Patient recruitment occurred from September 2018 to October 2023 at the N.N. Blokhin National Medical Research Center of Oncology.

Statistical Analysis

A prospective single-center phase II study with a two-stage Simon design [25, 26].

The primary endpoint was the rate of achieving therapeutic mitotane concentration.

Secondary endpoints included the ORR and DC ≥ 6 months, PFS, OS, and treatment safety.

The statistical hypothesis was that the proposed mitotane dosing regimen would increase the rate of achieving the target drug concentration level from 50 to 70 % with a power of 80 % and a significance level of $\alpha = 0.05$. The study objective was considered achieved if ≥ 27 of 43 evaluated patients reached the therapeutic mitotane concentration. Accounting for potential data loss, the sample size was set at 47 patients.

Procedures

The following procedures were performed for all patients before initiating therapy:

– Measurement of cortisol and ACTH levels after a low-dose dexamethasone suppression test (1 mg dexamethasone taken at 23:00 on the day before blood draw).

– Contrast-enhanced computed tomography of the chest, abdomen, and pelvis (performed no more than 4 weeks before therapy initiation).

In the presence of neurological symptoms, magnetic resonance imaging (MRI) of the brain with intravenous contrast was additionally performed. In cases of persistent arterial hypertension and/or hypokalemia, morning levels of aldosterone and renin were additionally measured. In women with signs of virilization, levels of dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, androstenedione, and total testosterone were assessed. In men with gynecomastia, estradiol levels were measured.

Treatment Regimen

The initial dose of mitotane was 2 g/day orally, divided into two doses, with gradual dose escalation every 3–5 days up to 4 g/day. Subsequently, the mitotane dose was adjusted based on its serum concentration to achieve and maintain a therapeutic level of 14–20 μg/mL. The maximum daily dose of mitotane was 8 g. The mitotane dosing regimen with dose escalation is presented in tab. 1.

Mitotane is to be taken orally strictly after meals. Since its bioavailability depends on the type of food consumed, it is recommended to take it after a high-fat meal (e.g., milk, chocolate, bread with butter).

The first measurement of mitotane blood concentration is performed on days 35–49, and subsequently every 4–6 weeks. The morning dose of

Table 1. Mitotane Dosing Regimen

Medication	Morning (tabs)	Noon (tabs)	Evening (tabs)
Mitotane 500 mg per tablet			
Days 1–3	2	0	2
Days 4–7	2	1	2
Days 8–10	2	2	2
Days 11–14	3	2	2
From Day 15 onwards	3	2	3

Table 2. Algorithm for mitotane dose adjustment based on its concentration and the presence of adverse events

Plasma Mitotane Concentration	Grade 2 Central Neurotoxicity / Grade 3–4 Gastrointestinal Adverse Events		Grade 3–4 central neurotoxicity
	Absent	Present	
< 14 μg/mL	Increase daily mitotane dose by 1 g	Reduce daily mitotane dose by 1 g	Temporarily discontinue mitotane until toxicity resolves. Upon resumption, reduce dose by 50–75 %.
14–20 μg/mL	Maintain current mitotane dose	Reduce daily mitotane dose by 1.5 g	—
> 20 μg/mL	Temporary discontinuation of mitotane may be considered for grade 1 central toxicity until resolution. Reduce daily dose by 50 %.	Temporarily discontinue mitotane until toxicity resolves. Upon resumption, reduce dose by 50 %.	Temporarily discontinue mitotane until toxicity resolves. Upon resumption, reduce dose by 50 %.

mitotane is omitted on the day of blood sampling. Further dose increases are made based on the blood concentration of mitotane (therapeutic range 14–20 mg/L):

– If the mitotane concentration is < 10 μg/mL at the first measurement and there is no significant central neurotoxicity, the daily dose is escalated by 1 g.

– If the mitotane concentration is < 14 μg/mL at the second and subsequent measurements and there is no significant central neurotoxicity, the daily dose is escalated by 1 g.

During mitotane therapy, daily monitoring of blood pressure (BP) and heart rate (HR) is recommended. Concentrations of mitotane, thyroid-stimulating hormone (TSH), free thyroxine (free T4), ACTH, cortisol, sodium, potassium, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are monitored every 4–6 weeks. A lipid profile (total cholesterol, HDL, LDL) is checked every 3 months.

All patients received standard platinum-based chemotherapy concurrently with mitotane treatment: EDP (etoposide 100 mg/m² IV infusion on days 2–4, doxorubicin 40 mg/m² IV on day 1, cisplatin 40 mg/m² IV on days 3–4; 28-day cycle) or EP (etoposide 100 mg/m² IV infusion on days 1–3, cisplatin 75 mg/m² IV on day 1; 21-day cycle) / EC (etoposide 100 mg/m² IV infusion on days 1–3, carboplatin AUC5 IV on day 1; 21-day cycle). If surgical treatment was deemed necessary after completion of chemotherapy, mitotane was discontinued 7–14 days before surgery and resumed 4–12 weeks after the procedure.

Concomitant Therapy

In all patients without ACTH-independent hypercortisolism, replacement therapy with hydrocortisone at a dose of 50 mg/day or equivalent doses of prednisolone (12.5 mg/day) was initiated from the first day of mitotane intake. In elderly patients with arterial hypertension or diabetes mellitus, the initial hydrocortisone dose was 30 mg/day. The daily hydrocortisone dose was divided into three parts — two-thirds in the morning hours (upon waking and around noon, ~ 12:00) and one-third in the evening (optimal intake time between 17:00–18:00). Subsequently, the hydrocortisone dose was increased in increments of 20 mg if laboratory or clinical signs of adrenal insufficiency appeared. In most patients, the daily hydrocortisone dose during mitotane therapy was 50–70 mg.

In patients with hypercortisolism, hydrocortisone replacement therapy was initiated only after the appearance of laboratory or clinical signs of adrenal insufficiency.

In the presence of hyperaldosteronism, spironolactone was prescribed at an initial dose of 100 mg per day; if insufficiently effective (persistent hypokalemia < 3.0 mmol/L), the spironolactone dose was escalated to 300 mg per day.

All patients assigned to the EDP chemotherapy regimen received primary prophylaxis for febrile neutropenia with granulocyte colony-stimulating factor (G-CSF) — filgrastim. All patients received

triple antiemetic therapy with the addition of olanzapine or aprepitant/fosaprepitant.

Efficacy Assessment

For response assessment, contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis was performed at baseline, then every 6–8 weeks for the first 6 months, and subsequently every 9–12 weeks.

The Kaplan — Meier method with the log-rank test for curve comparison was used to assess PFS and OS. Statistical calculations were performed using IBM SPSS Statistics Professional 27.0.

Safety Assessment

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.05. In case of grade 3–4 non-hematological toxicity, chemotherapy and mitotane were temporarily discontinued until the severity of the adverse event resolved to grade ≤ 1. The algorithm for mitotane dose adjustment is provided in tab.2.

Table 3. Patient Characteristics

Characteristic	N	%
Sex		
Male	27	57.4
Female	20	42.6
Stage at study inclusion		
III (ENSAT)	1	2.1
IV	46	97.9
Median age (years)	43 (19–64)	
ECOG Performance Status		
0	26	55.3
1	21	44.7
Hormonal Secretion		
No	25	53.2
Cortisol	18	38.2
Aldosterone	1	2.1
Sex Hormones	3	6.4
Recurrence-free interval after adrenalectomy		
< 1 year	8	17.0
≥ 1 year	13	27.7
De novo metastatic disease	26	55.3
Ki-67 Index		
0–10 %	9	19.1
11–20 %	12	25.5
> 20 %	21	44.7
No data	5	10.6
Sites of Metastases		
Lungs	30	63.8
Liver	22	46.8
Peritoneum	14	29.8
Brain	1	2.1
Number of Metastatic Sites		
1	12	25.6
2	19	40.4
≥ 3	16	34.0
Chemotherapy Regimen		
EDP	45	95.8
EP	1	2.1
EC	1	2.1

Results

Patient Characteristics

A total of 47 patients were enrolled in the study, including 27 men (57.4 %) and 20 women (42.6 %). The median age was 43 years (range 19–64). ECOG performance status of 0 was reported for 26 patients (55.3 %).

More than half of the patients (55.3 %, n = 26) had de novo metastatic ACC. Hormonal secretion was observed in half of the patients (46.8 %, n = 22), with hypercortisolism being the most frequent endocrine disorder — 38.2 % (n = 18), hypersecretion of sex hormones was observed in 6.4 % of cases (n = 3), and hyperaldosteronism in 1 (2.1 %) case.

The most common metastatic sites were the lungs at 63.8 % (n = 30) and the liver at 46.8 % (n = 22). Brain metastases were detected in 1 patient (2.1 %). In 12 (34 %) cases, metastases were observed in ≥ 3 sites.

The Ki-67 index was determined in the primary tumor for 36 patients (76.6 %) and in a metastasis for 11 (23.4 %). A high Ki-67 level (> 20 %) was observed in 21 (44.7 %) cases (tab. 3).

Treatment Efficacy

At a median follow-up of 12.4 months, treatment efficacy and therapeutic mitotane concentration were evaluated in all 47 cases. Therapeutic mitotane concentration was achieved in 34 patients (72.3 %), in accordance with the statistical hypothesis the study is positive — the primary endpoint was reached.

The median time to achieve therapeutic concentration was 4.3 months (95 % CI, 3.3–5.26 months), fig. 1.

An objective response was achieved in 14 patients (29.7 %), all cases were partial responses. Disease stabilization was observed in 19 (43.2 %), disease control ≥ 6 months — in 30 (63.8 %), fig. 2.

Surgical treatment after completion of chemotherapy was performed in 7 patients (14.9 %), with R0 resection in 6 cases and R2 in 1 case.

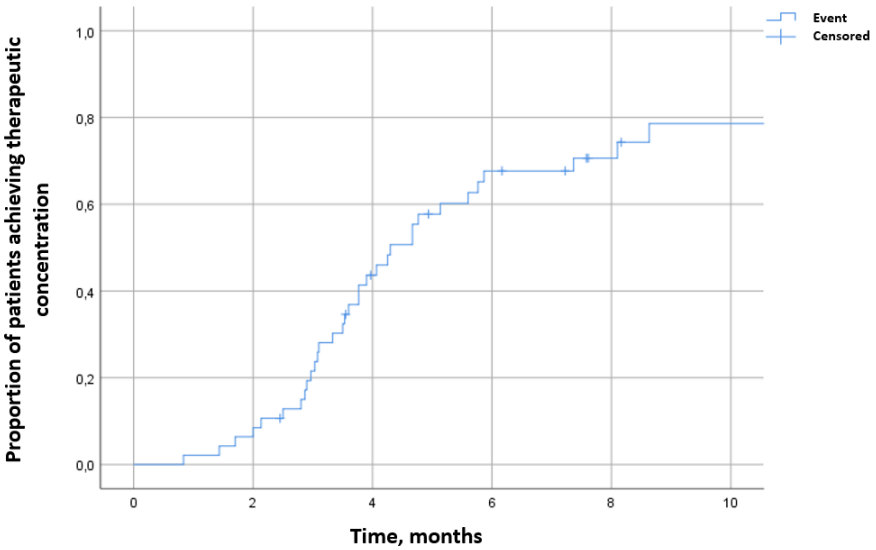

Fig. 1. Time to achieve therapeutic mitotane concentration

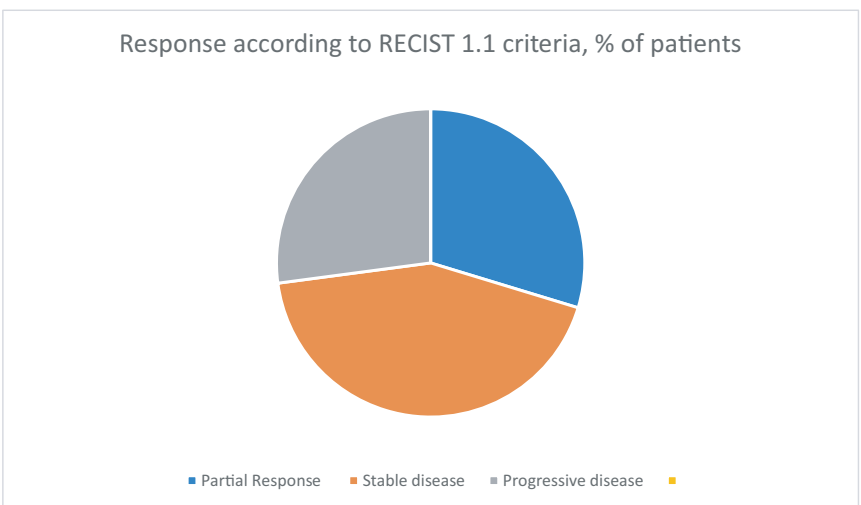

Fig. 2. Patient response according to RECIST 1.1 criteria

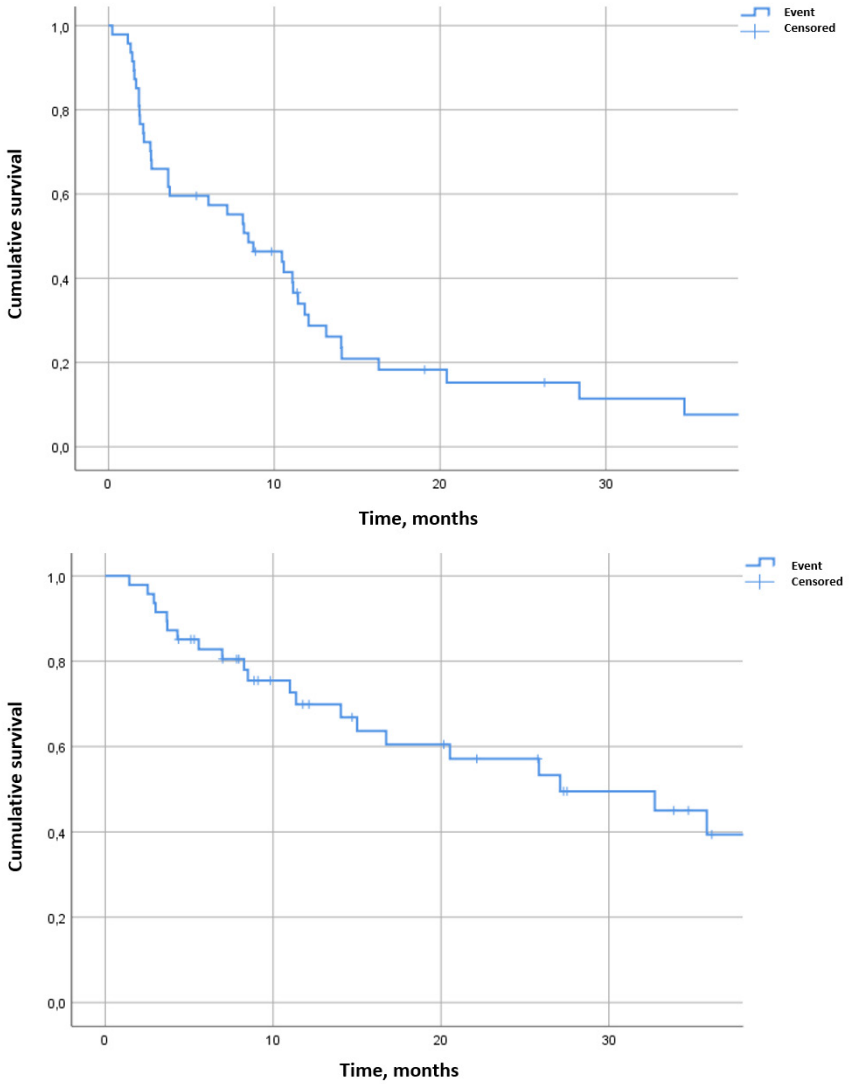

Fig. 3. A) Progression-free survival; B) Overall survival

Table 4. Most common adverse events during platinum-based chemotherapy combined with mitotane

Adverse Event	Any grade, N	Any grade, %	Grade 3–4, N	Grade 3–4, %
Any adverse event	47	100	12	25.5
Adrenal insufficiency	not assessed		1	2.1
Hyperkalemia	4	8.5	1	2.1
Neutropenia	45	95.7	12	25.5
Febrile neutropenia	2	4.3	3	6.4
Anemia	46	97.9	7	14.9
Thrombocytopenia	8	17.0	0	0
Nausea	46	97.9	3	6.4
Diarrhea	7	14.9	0	0
Vomiting	9	19.1	2	4.3
Hepatotoxicity	3	6.4	2	4.3
Asthenia	47	100	4	8.5
Central neurotoxicity	24	51.1	1	2.1
Sensory polyneuropathy	3	6.4	0	0
Hypothyroidism	6	12.8	0	0
Venous thromboembolic events	3	6.4	1	2.1
Infusion reactions	1	2.1	0	0

Median PFS was 8.44 months (95 % CI, 4.2–12.6) (fig. 3, A). Median OS was 24.3 months (95 % CI, 9.9–44.6) (fig. 3, B).

Treatment Safety

Adverse events (AEs) of any grade were observed in 100 % of patients, grade 3–4 AEs in 12 (25.5 %). Serious AEs leading to emergency hospitalization were recorded in 3 patients (6.4 %), including 1 case of adrenal insufficiency, 1 case of pulmonary embolism, and 1 case of febrile neutropenia.

Central neurotoxicity of any grade was documented in 24 patients (51.1 %), including grade 3 in 1 case (2.1 %) (tab. 4).

Discussion

Despite the widespread use of mitotane in the therapy of adrenocortical carcinoma (ACC), standardized approaches to its administration that allow achieving therapeutic drug concentrations in the majority of patients have been lacking to date. The data from our prospective study demonstrated that the proposed regimen of mitotane dose escalation against the background of platinum-based chemotherapy enables achieving therapeutic concentrations in 72.3 % of patients. This exceeds the values previously obtained in multicenter and adjuvant studies (52–59 %) and is comparable to the results achieved in retrospective studies conducted in reference centers [10, 13]. The median time to achieve therapeutic concentration obtained in our study was 4.3 months, which is comparable to retrospective data [27]. It should be emphasized that achieving therapeutic mitotane concentration is associated with improved PFS and OS in a number of retrospective works, making this parameter an important intermediate endpoint in clinical trials of ACC.

The ORR and DC were comparable to the results of the FIRM-ACT study and somewhat lower than in one of the largest retrospective studies conducted by a European group (ORR 55 %) [28–30]. The survival rates (PFS, OS) were comparable to those previously published works [28–30].

The safety profile observed in the study corresponded to previously published data and was manageable. In our study, only 1 case (2 %) of grade 3 adrenal insufficiency was recorded. The low incidence of severe adrenal insufficiency is associated with the timely prescription and adjustment of hydrocortisone replacement therapy from the first day of mitotane intake in all patients without hypercortisolism.

Conclusion

These findings demonstrate that the mitotane dosing regimen developed in our study enables the achievement of target concentrations in the majority of patients, is characterized by an acceptable toxicity profile and high clinical efficacy.

Study Limitations

The main limitation of this study is its small sample size, which is due to the rarity of the disease.

Conflict of Interest

The authors declare no conflict of interest.

Compliance with patient rights and principles of bioethics

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants.

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The study was performed without external funding.

Authors' contributions

All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published.

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