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RESEARCH

Mitotane dosage, plasma levels, and anthropometric measurements in pediatric adrenocortical carcinoma

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Abstract

Objective: Mitotane is an effective treatment for advanced adrenocortical carcinoma (ACC). Given the limited pediatric data available, this study aims to evaluate the associations between mitotane dosage, plasma drug levels, and anthropometric measurements, as well as their potential impact on dosage requirements to optimize therapeutic outcomes in pediatric patients with ACC (pACC).

Design and methods: A retrospective, international, multicenter study was conducted on pediatric ACC patients treated with mitotane across 18 centers. Mitotane serum levels were obtained from the Lysosafe Online® database or directly from the centers. Data from the cohort with plasma levels within the target range (≥14 mg/L; *n* = 319) were analyzed and compared to those with levels outside this range (*n* = 320).

Results: Fifty pediatric patients (60% female) diagnosed between 2004 and 2023 were included, with a median follow-up of 34.5 months and a 10-year overall survival of 33 months. The median age at diagnosis was 8.6 years, with most tumors (84%) hormone-secreting. Among 49 patients undergoing surgery, 31 (62%) achieved R0 resection. The median treatment duration was 18 months, with a median mitotane dose of 87 mg/kg/day in patients within the target plasma level range, showing no significant difference from those outside the range. However, BMI was significantly associated with doses of plasma levels in target range ($P = 0.001$), as underweight (105.4 mg/kg/day) and healthy weight patients (98.4 mg/kg/day) required higher doses than overweight/obese patients (44.4 mg/kg/day). No significant differences in daily dose levels (mg/kg/day and mg/m^2/day) were observed based on body weight.

Conclusion: This study supports estimating mitotane dosages in pediatric ACC, emphasizing the need for close monitoring and frequent follow-ups at specialized centers due to individualized dosing and a narrow therapeutic window.

Keywords: pediatric adrenocortical carcinoma; mitotane; pediatric adrenocortical tumor; mitotane dosage; mitotane plasma level

Introduction

Pediatric adrenocortical carcinoma (pACC) is an exceptionally rare malignancy, with an incidence of 0.2–0.3 cases per million children under the age of 20 per year (1, 2) and differs clinically and histopathologically from adult ACC tumors (3, 4, 5, 6, 7). The prognosis for patients with advanced pACC is unfavorable, and effective risk stratification remains a subject of ongoing debate (8, 9, 10, 11).

En bloc surgical resection of the tumor is the primary and most effective treatment for pediatric adrenocortical carcinoma, with complete tumor removal leading to a cure in most cases (9, 12, 13, 14). In addition, systemic therapy is indicated for advanced tumor stages with a high risk of recurrence (9, 12, 15, 16). Since prospective clinical randomized trials are lacking so far, systemic treatment regimens remain highly heterogeneous. Following the recommendations of the Children's Oncology Group (COG) (12) and the German GPOH-MET 97 strategy (17), the most commonly used chemotherapeutics to date are cisplatin, etoposide, and doxorubicin (EDP).

In addition to chemotherapy, mitotane – an antineoplastic agent with specific adrenocortical activity – is clearly indicated in pACC patients with advanced stages (III-IV), incomplete tumor resection, tumor spillage, or primary unresectable tumors. In patients with stage II disease, the indication for mitotane therapy depends on the clinical course and tumor-specific characteristics; for example, a high Ki-67 index has been discussed as a potential factor supporting mitotane treatment, although evidence remains limited (9, 15, 18, 19).

However, not all patients have access to mitotane treatment in every country, and the evaluation of mitotane plasma levels is not always feasible. Given the limited evidence from studies on mitotane treatment in pACC, the recently published international expert consensus recommends close monitoring of mitotane serum levels in pACC patients, with a target plasma range of 14–20 mg/L (9, 12, 16, 17, 18, 20). The recommended standard duration of mitotane treatment in children – depending on clinical response and tolerability – is 24 months, with a minimum treatment

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duration of at least 1 year (18). Adverse effects during mitotane therapy are frequent and encompass a broad spectrum of clinical manifestations, including hematological, endocrinological, gastrointestinal, and neurological toxicities. Especially neurological adverse effects (e.g., ataxia, confusion, and dizziness) show a strong correlation with elevated plasma concentrations and may be life-threatening, underscoring the importance of regular monitoring of mitotane blood levels, along with close clinical and neurological surveillance, to ensure early detection and prevention of toxicity (15, 18, 21, 22, 23, 24, 25, 26).

Given the limited understanding of pharmacokinetic correlations of mitotane in pACC patients, this study aims to evaluate the associations between mitotane dosage, plasma drug levels, and anthropometric measurements, and their potential impact on dosage requirements to optimize therapeutic outcomes.

Methods

For this international multicenter study, data from 50 pediatric patients with adrenocortical carcinoma treated with mitotane were retrospectively collected from 18 centers across 10 countries (Germany, Brazil, Spain, Poland, Netherlands, Turkey, Algeria, Italy, Austria, and Finland).

Inclusion criteria for the analyses of the cohort were histopathologically confirmed diagnosis of ACC according to the Wieneke criteria (27), treatment with mitotane, availability of at least three mitotane plasma levels, and follow-up data. Patients were staged using the TNM/ENSAT (28) and COG staging systems (12).

Consistent with the previous literature, a mitotane plasma level of ≥14 mg/L was defined as the threshold, representing the lower limit of the target range established in several studies (9, 12, 16, 17, 18, 20). For body mass index (BMI) calculation, the official WHO BMI classification was used with slight modification, as overweight and obese patients were combined into a single group due to limited patient numbers: underweight <18.5 kg/m^2, healthy weight 18.5–24.9 kg/m^2, and overweight/obesity ≥25.0 kg/m^2.

Some of the mitotane concentration levels and dosages were directly obtained from the centers where the patients were treated. However, the majority of the concentrations were collected from the Lysosafe Online® database (www.lysosafe.com), a secure online platform designed for determining, monitoring, and managing mitotane levels in patients with ACC. This platform allows registered physicians to collect, store, and analyze pseudonymized patient data related to mitotane concentrations, ensuring that the drug is administered at therapeutic levels while minimizing toxicity. The collaborating centers took screenshots of the pseudonymized mitotane plasma levels and dosages from the Lysosafe Online® database and sent them via email.

Due to the differing standards for monitoring plasma levels across treatment centers during mitotane therapy, the frequency of available plasma level measurements varied. In addition, a few patients (n = 3–4) were still receiving mitotane treatment at the end of the data collection period. For pediatric patients undergoing mitotane therapy, the dosage was commonly administered based on body weight.

The project received approval from the Würzburg local ethics committee (20231016 02, Würzburg, Germany 2023).

Statistical analyses were performed using R Studio to evaluate the findings of the study. The Kolmogorov–Smirnov test was used to determine the normality of the distribution of the parameters. Descriptive statistical methods (mean, median, range) were applied, and the Mann–Whitney U test was used for comparisons between groups with non-normally distributed parameters. The Spearman's rho correlation coefficient was calculated to analyze the relationship between two continuous variables. The relationship between the two variables was modeled using linear regression analysis. Chi-square test and Fisher's exact test were used for comparison of qualitative data. Survival curves were constructed by the Kaplan–Meier method, and the results were compared by univariate and multivariate Cox regression analysis. Results are presented as hazard ratio with 95% confidence intervals (95% CI). Statistical significance was conventionally set at $P < 0.05$.

Results

Patients' baseline characteristics

This study included 50 pediatric patients diagnosed with adrenocortical carcinoma between 2004 and 2023 and treated with mitotane. The median age at diagnosis was 107 months (range: 1–241 months), with 12 patients (24%) being younger than 4 years. The gender distribution was nearly equal, with a slight predominance of female patients (n = 3, 60%). The majority of patients (84%) had hormone-secreting tumors, with androgen-secreting tumors being the most common (n = 23, 46%). Among patients with available genomic testing results, 11 of 27 (41%) were diagnosed with a cancer predisposition syndrome, specifically Li-Fraumeni syndrome. Given that mitotane is typically administered in advanced tumor stages, 35 patients (70%) presented with stage 3 or 4 tumors, while 13 patients had tumors in earlier stages. Most of these patients had additional risk factors, such as tumor spillage, incomplete resection, or a high Ki-67 index, which contributed to the decision to pursue more intensive therapy on an individual basis. Almost half of the patients (n = 24, 48%) had tumors

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Table 1 Baseline characteristics of an international, multicenter pediatric ACC cohort.

Clinical characteristics*		Patients (*n* = 50)
Age at diagnosis	Median/mean/range (months)	107/107.5/1–241
(*n*; %)	<4 years	12; 24
	4–11.9 years	20; 40
	12–18 years	15; 30
	>18 years	3; 6
Sex (*n*; %)	Female	30; 60
	Male	20; 40
Hormonal secretion (*n*; %)	No	5; 10
	Mixed	10; 20
	Androgen	23; 46
	Glucocorticoid	9; 18
	No information available	3; 6
Tumor stage (*n*; %)	I	2; 4
	II	11; 22
	III	15; 30
	IV	20; 40
	No information available	2; 4
Ki-67 status/rate of mitosis (*n*; %)	Low; 0–9%	5; 10
	Intermediate; 10–19%	1; 14
	High; ≥20%	24; 48
	No information available	14; 28
Resection status (*n*; %)	R0	31; 62
	R1	5; 10
	R2	8; 16
	Not resected	1; 2
	Spillage	4; 8
	No information available	1; 2
Radiotherapy (*n*; %)	No	36; 72
	Yes	11; 22
	No information available	3; 6
Relapse/tumor progression (*n*; %)	No	25; 50
	Yes	24; 48
	No information available	1; 2
Long-term outcome (*n*; %)	No evidence of disease	24; 48
	Alive with disease	10; 20
	Dead of disease	16; 32
Follow-up (months)	Median/mean/range	34.5/45.3/2–187
10-year OS (months)	Median/mean/range	33/42.5/2–120
Duration of mitotane treatment (months)	Median/mean/range	18/20.4/2–60
Brazilian cohort (*n*; %)	No	42; 84
	Yes	8; 16
pS-GRAS groups (*n*; %)	1	10; 20
	2	16; 32
	3	3; 6
	4	1; 2
Treatment (*n*; %)	Mitotane	7; 14
	Mitotane + chemotherapy	40; 80
	No information available	3; 6
Body weight (*n*; %)	0–9 kg	3; 6.4
	10–19 kg	8; 17
	≥20 kg	35; 75
	No information available	1; 2.1
BMI classification (*n*; %)	Underweight (<18.5 kg/m^2)	22; 47
	Healthy weight (18.5–24.9 kg/m^2)	14; 30
	Overweight/obesity (≥25 kg/m^2)	10; 21
	No information available	1; 2
Cancer predisposition syndrome (*n*; %)	Yes	11; 22
	No	16; 32
	No information available	23; 46

*Clinical characteristics including number of patients (*n*), age at diagnosis, sex, hormonal secretion, tumor stage, Ki-67 status/rate of mitosis, resection status, radiotherapy, relapse/tumor progression, long-term outcome, follow-up time, 10-year OS (overall survival), duration of mitotane treatment, number of the Brazilian cohort, pS-GRAS groups, treatment, body weight, BMI classification, and cancer predisposition syndrome (in total *n* and %).

characterized by a high mitotic rate, with Ki-67 ≥ 20%. All but one patient underwent primary surgical intervention, with 31 patients (62%) achieving R0 resection. However, incomplete resection (R1 and R2) was observed in 13 patients (26%), and tumor spillage occurred in 4 patients (8%). The median treatment duration of mitotane was 18 months (ranging from 2 to 60 months). Roughly 25% of the patients were of Brazilian origin. While most patients had a total body weight of ≥20 kg (75%), nearly half of the cohort (47%) was classified as underweight based on a BMI < 18.5 kg/m^2 (for details see Table 1).

The follow-up period was 34.5 months in the median (range: 2–187 months), and the 10-year overall survival (OS) was 33 months. During long-term follow-up, 24 patients (48%) experienced a relapse or tumor progression. At the last follow-up, 24 patients (48%) had no evidence of disease, 10 patients (20%) were alive with disease, and 16 patients (32%) had died of disease (see Table 1).

Patients were divided into two treatment groups based on the therapeutic approach. Seven patients received mitotane monotherapy, while forty patients underwent combination therapy with mitotane and chemotherapy, mostly utilizing the EDP-M regimen (etoposide, cisplatin, doxorubicin, and mitotane). Data on chemotherapy were unavailable for three patients. The group that received both mitotane

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Table 2 Analysis of clinical characteristics by treatment groups.

Clinical characteristics[1] (*n* = 47)[2]		Mitotane (*n* = 7)	Mitotane + chemotherapy (*n* = 40)	*P*
Age at diagnosis	Median/mean/range (months)	60/89.9/26–199	108/109.6/1–241	0.472[3]
(*n*; %)	<4 years	3; 42.9	8; 20	0.330[4]
	≥4 years	4; 57.1	32; 80	
Sex (*n*; %)	Female	3; 42.9	24; 60	0.438[4]
	Male	4; 57.1	16; 40	
Hormonal secretion (*n*; %)	No	0; 0	5; 12.8	0.587[5]
	Mixed	0; 0	10; 39	
	Androgen	4; 66.7	17; 43.6	
	Glucocorticoid	2; 33.3	7; 17.9	
Tumor stage (*n*; %)	I	0; 0	1; 2.6	0.097[5]
	II	4; 57.1	6; 15.8	
	III	2; 28.6	13; 34.2	
	IV	1; 14.3	18; 47.4	
Ki-67 status/rate of mitosis (*n*; %)	Low; 0–9%	1; 20	3; 10.7	0.385[5]
	Intermediate; 10–19%	2; 40	5; 17.9	
	High; ≥20%	2; 40	20; 71.4	
Resection status (*n*; %)	R0	7; 100	21; 53.8	0.257[5]
	R1	0; 0	5; 12.8	
	R2	0; 0	8; 20.5	
	Not resected	0; 0	1; 2.6	
	Spillage	0; 0	4; 10.3	
Radiotherapy (*n*; %)	No	7; 100	28; 73.7	0.320[4]
	Yes	0; 0	10; 26.3	
Relapse/tumor progression (*n*; %)	No	7; 100	16; 41	0.009[4,**]
	Yes	0; 0	23; 59	
Long-term outcome (*n*; %)	No evidence of disease	7; 100	15; 37.5	0.009[5,**]
	Alive with disease	0; 0	10; 25	
	Dead of disease	0; 0	15; 37.5	
Follow-up (months)	Median/mean/range	80/91.4/8–187	27/37.3/2–135	0.026[3,*]
Duration of mitotane treatment (months)	Median/mean/range	24/24.3/8–60	17.5/20.2/2–60	0.508[3]
Brazilian cohort (*n*; %)	No	6; 85.7	33; 82.5	1.000[4]
	Yes	1; 14.3	7; 17.5	
pS-GRAS criteria (*n*; %)	1	3; 75	6; 25	0.257[5]
	2	1; 25	14; 58.3	
	3	0; 0	3; 12.5	
	4	0; 0	1; 4.2	
Cancer predisposition syndrome (*n*; %)	Yes	1; 20	10; 47.6	0.356[4]
	No	4; 80	11; 52.4	

[1]Clinical characteristics comparing the two treatment groups: mitotane alone vs mitotane plus chemotherapy. [2]Three of 50 patients were excluded from the treatment subgroup analysis due to the unavailability of chemotherapy data. [3]Mann–Whitney U test. [4]Fisher's exact test. [5]Pearson Ki-Kare test. *P < 0.05. **P < 0.01.

and chemotherapy exhibited significantly higher rates of relapse and disease-related mortality (P < 0.01). When evaluated using the recent prognostic scoring recommendations for pACC patients (pS-GRAS) (8), the group receiving both mitotane and chemotherapy tended to fall into higher risk groups compared to the group treated with mitotane monotherapy (see Table 2 for details).

Dosages of mitotane in relation to anthropometric measurements and mitotane therapeutic plasma levels

Evaluation of mitotane dosage in the pediatric cohort – comprising 670 measurements from 47 patients with available treatment data – revealed a significant positive correlation between mitotane dosage and body weight, body length, body surface area (BSA), and BMI at the start of treatment (P = 0.001) (see Table 3).

To determine the optimal average mitotane dosage in pediatric patients and to investigate potential differences in dosages between patients with plasma levels within and outside the target range, data from the pediatric cohort with plasma levels within the target range (≥14 mg/L; n = 319) were analyzed and compared to those with levels outside this range (n = 320). The median dose of values in the target range was 87.2 mg/kg/d (ranging from 6.0 to 11,255.0 mg/kg/d) and 1,802.8 mg/m^2/d (ranging from 126.0 to 1,664.0 mg/m^2/d). The median dose of values outside the target range did not differ significantly (see Table 4).

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Table 3 Correlation of mitotane dosage and anthropometric measurements in pACC patients.

	Mitotane dosage (mg/day)[1]	
	r_s	*P*-value
Body weight at start of mitotane (kg)	0.526	0.001**
Body length at start of mitotane (cm)	0.625	0.001**
Body surface area (BSA) at start of mitotane (m^2)	0.534	0.001**
BMI (kg/m^2)	0.212	0.001**

[1]Correlation of mitotane dosage (mg/day) and body weight (kg), body length (cm), body surface area (BSA) (m^2), and BMI (kg/m^2) of pACC patients (*n* patients = 47, *n* measurements = 670) at the start of mitotane treatment using Spearman's rho correlation coefficient (**P < 0.01, *P < 0.05).

To assess the influence of individual anthropometric measurements on mitotane dosages and plasma levels, all plasma level values within the target range (≥14 mg/L) from the patient cohort (*n* = 47) were grouped according to body weight (0–9 kg, 10–19 kg, ≥20 kg) and BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, ≥25.0 kg/m^2). No significant differences in daily dosage levels (mg/kg/day and mg/m^2/day) were observed based on body weight, although children and toddlers with lower weights (0–9 kg) tended to require higher mitotane dosages compared to those with higher body weights (see Table 5). However, when examining BMI, a statistically significant difference in dosage (mg/kg/day) was found (P = 0.001): the Mann–Whitney U test showed that the median dosages for the underweight group (105.4 mg/kg/day) and the healthy weight group (98.4 mg/kg/day) were significantly higher than those for the overweight/obese group (44.4 mg/kg/day). No significant difference was observed between the underweight and healthy weight groups (see Table 5).

Discussion

Besides surgical resection and systemic chemotherapy, mitotane is an effective and approved pillar of treatment in adult and pediatric patients with advanced ACC (9, 12, 15, 16, 17, 18, 29, 30). The recommended starting dose of mitotane for children is 50 mg/kg/day or 1,500 mg/m^2/day, with the possibility of increasing the dose to a maximum of 4,000 mg/m^2/day (18). Like many other drugs, mitotane is metabolized in the liver via cytochrome P450 enzyme CYP3A4 and also induces its activity (31, 32, 33). However, CYP3A4 activity varies significantly between individuals due to genetic, physiological, and pharmacological factors (34, 35). This aligns with our findings, as mitotane dosages varied significantly among individual patients, and those outside the therapeutic target range received dosages similar to those within the range. In addition, age is an important determinant of CYP3A4 function, as enzyme activity is reduced during the first months of life due to immature hepatic expression, with adult CYP3A4 levels reached between 1 and 1.5 years of age (36, 37, 38). No significant differences were observed between weight groups; however, these findings are limited by the small cohort size, particularly the low number of infants. Further studies with larger cohorts are warranted to investigate the age dependency of mitotane dosing more robustly.

Mitotane is a lipophilic drug, resulting in extensive distribution into adipose tissue. In obese patients, the increased fat mass leads to a larger volume of distribution, which prolongs the time required to reach therapeutic target levels. Once the therapeutic target level is achieved, the maintenance dose should be carefully adjusted, as obesity contributes to mitotane's prolonged half-life and delayed kinetics, increasing the risk of drug accumulation and toxicity (32, 39, 40, 41). When analyzing the association between BMI and mitotane dosage in the current pediatric cohort, a statistically significant difference was observed in dosages within the therapeutic target range. Specifically, patients in the underweight/healthy-weight group (BMI < 25 kg/m^2) received significantly higher doses compared to those in the overweight/obese group (BMI ≥ 25 kg/m^2). This finding highlights the role of mitotane accumulation in adipose tissue, which leads to lower required dosages once the therapeutic target level is reached, especially considering that most patients received mitotane treatment for an extended period, with a median duration of 18 months.

Major limitations of the study were the small number of patients, the retrospective character of the study, and the international and multicenter nature of the study, leading to variations in treatment and follow-up protocols.

Table 4 Mitotane dosage evaluation according to plasma level of pACC patients.

	Mitotane plasma level (mg/L)[1]		
Dosage	<14 mg/L (*n* measurements = 320) Median (min–max)	≥14 mg/L (*n* measurements = 319) Median (min–max)	*P*
mg/d	4,000.0 (60.0–13,000.0)	3,500.0 (50.0–13,000.0)	0.438
mg/kg/d	87.5 (7.2–1,125.0)	87.2 (6.0–1,125.0)	0.872
mg/m^2/d	1,854.6 (151.1–16,642.0)	1,802.8 (126.0–16,642.0)	0.414

[1]Mitotane dosage evaluation (in mg/day, mg/kg/day, and mg/m^2/day) for the two groups of pACC patients (*n* patients = 47, *n* measurements plasma level = 639) with mitotane plasma levels <14 mg/L and ≥14 mg/L, analyzed using the Mann–Whitney U test.

Table 5 Mitotane dosage evaluation according to anthropometric measurements within target plasma range.

	Body weight[1]			
Dosage	**0–9 kg (*n* value = 18) Median (min–max)**	**10–19 kg (*n* value = 57) Median (min–max)**	**≥20 kg (*n* value = 234) Median (min–max)**	***P***
mg/d	900.0 (50.0–4,500.0)	1,500.0 (400.0–4,000.0)	4,000 (500–13,000)	0.001**
mg/kg/d	108.4 (6.02–1,125.0)	79.4 (26.7–267.7)	92.4 (7.3–300.0)	0.928
mg/m²/d	2,267.6 (125.9–16,642.0)	1,239.7 (356.0–4,385.8)	1,893.8 (183.7–4,057.3)	0.190
	BMI classification[1]			
	Underweight (<18.5 kg/m²) (*n* value = 138)	**Healthy weight (18.5–24.9 kg/m²) (*n* value = 110)**	**Overweight/obesity (≥25.0 kg/m²) (*n* value = 61)**	
mg/d	2,500.0 (400.0–9,000.0)	4,000.0 (50.0–13,000.0)	4,500.0 (500–9,000)	0.001**
mg/kg/d	105.4 (22.7–1,125.0)	98.4 (6.0–397.6)	44.44 (7.3–142.9)	0.001**
mg/m²/d	1,788.9 (356.0–16,624.0)	1,936.9 (126.0–8,314.4)	1,314.8 (183.7–3,794.9)	0.109

[1]Mitotane dosage evaluation (in mg/day, mg/kg/day, and mg/m²/day) for the three different body weight groups and BMI classification of the pACC patient cohort (*n* = 46, because weight information is missing for one patient, *n* measurements of plasma level = 309). The analysis was done with patient values only within the target plasma range of ≥14 mg/L using the Kruskal–Wallis test (**$P < 0.01$, *$P < 0.05$). The Mann–Whitney U test was used for pairwise comparisons.

Nevertheless, the authors are convinced that, despite its limitations, the existing data provide essential insights into the treatment with mitotane in a pediatric cohort and will serve as a foundation for prospective studies already planned in this field.

In summary, this study aims to support the estimation of required mitotane dosages throughout the treatment course in pediatric ACC patients. However, due to the highly individualized dosage requirements and the narrow therapeutic window, precise dosing remains challenging. Therefore, close, frequent follow-up visits with therapeutic drug monitoring at specialized pediatric ACC treatment centers – particularly at the initiation of mitotane therapy – are essential for optimizing individualized treatment.

A second part of the current study was based on the multivariable analysis of adult patients conducted by Puglisi *et al.*, which demonstrated that both the time required to reach the target plasma range of ≥14 mg/L and the duration of mitotane plasma levels maintained within this range (=time in target range, TTR) significantly influence the risk of recurrence (42, 43). Accordingly, a cut-off value for TTR of >37.8 weeks was identified for the current pediatric cohort. This cut-off was used to stratify patients according to their mortality risk, indicating that a TTR >37.8 weeks is associated with a lower risk of death (see Supplementary Tables 1 and 2, and Supplementary Fig. 1 (see section on Supplementary materials given at the end of the article). The study focused on the primary outcome OS, defined as the time from the initial diagnosis to death or the last follow-up. Although TTR appeared to influence patient OS, no significant difference was observed in the univariable or multivariable analyses. We assume this lack of significance is due to the very limited number of patients included in the survival analysis. Another limitation is that patients in advanced stages often die of disease early during treatment, making it difficult to draw definitive conclusions about the optimal treatment duration and its threshold. In addition to TTR, a relationship was found between the time needed to achieve the first target level (with a cut-off defined as < 15.8 weeks) and patient outcomes, suggesting that patients benefit from a quicker attainment of mitotane levels within the target range (see Supplementary Tables 1 and 2, and Supplementary Fig. 1). Similar to TTR, no significant differences were observed between the two groups. Given the limited statistical power of the small pediatric cohort, these results are included only in the Supplementary materials as preliminary findings and will be evaluated in further prospective studies.

Although definitive conclusions cannot be drawn, these results reinforce the importance of adequate mitotane treatment duration and close follow-up in specialized centers to maintain target drug levels in pACC patients. To improve long-term treatment strategies, larger international studies with standardized data are needed. A centralized system linking mitotane plasma levels with clinical data would be a valuable tool for optimizing therapy and ensuring patient safety. To achieve this goal – which will substantially advance the understanding of treatment – collaborative efforts and initiatives are already in progress.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EO-24-0081.

Declaration of interest

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

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Author contribution statement

MR and WV conceived the study and wrote the paper, HF, MR, SRA, GFLC, CFC, NDP, JF, SF, MF, MG, MPH, CH, DJ, AJ, RRK, TK, MM, JM, MVN, SHP, TP, SP, PGS, VBB, GT, JW, BY, and VW collected data, MR, VW, and NÖK performed experiments and analyzed data statistically. All authors revised the manuscript.

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