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Case series

ADVERSE EVENTS RELATED TO MITOTANE DURING TREATMENT OF ADRENOCORTICAL CARCINOMA

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Abstract

Mitotane is a drug widely indicated in patients with adrenocortical carcinoma. Several adverse events related to mitotane have been reported in 30 to 90% of patients. We present a case series of toxicities related to mitotane therapy and their management. Clinical and laboratory examinations to detect adverse events were carried out at baseline, monthly for the first six months and quarterly afterwards. Mitotane blood concentrations were measured by liquid chromatography.

Six patients diagnosed with adrenocortical carcinoma and treated with mitotane were included, with hormone overproduction in four of them. Median time of follow up during mitotane therapy was 13 months [5-36]. All had adverse events related to mitotane detected during the first three months of treatment (median mitotane dose at first adverse event: 2 g/day). Four patients presented two or more adverse events. Endocrine side effects were the most frequently found (adrenal insufficiency, followed by hypothyroidism and hypercholesterolemia in order of frequency). Replacement therapy and/or statin treatment was prescribed as needed. Mitotane blood concentration in 3 of 4 patients was below the optimal range.

Treatment with mitotane requires individualized care to mitigate the risks of adverse events, optimize therapeutic outcomes, and ensure patient safety.

Key words: adrenocortical carcinoma, mitotane, adverse effects, adrenal gland neoplasms, adrenal insufficiency, hormone-dependent.

Resumen

Eventos adversos relacionados con mitotano durante el tratamiento del carcinoma adrenocortical

Mitotano es una droga indicada en pacientes con carcinoma adrenocortical. Se han reportado múltiples efectos adversos relacionados a este fármaco en 30 a 90% de los casos. Presentamos una serie de casos de toxicidades relacionadas al tratamiento con mitotano y su manejo. Los datos clínicos y de laboratorio para detección de eventos adversos fueron evaluados al inicio, mensualmente por los primeros seis meses y luego trimestralmente. Las concentraciones de mitotano fueron determinadas por cromatografía liquida. Seis pacientes fueron diagnosticados con carcinoma adrenal y tratados con mitotano, 4 de ellos con tumores funcionantes. La mediana de tiempo de seguimiento durante el tratamiento con mitotano fue de 13 meses [5–36]. Todos presentaron eventos adversos asociados a la droga, diagnosticados en los primeros tres meses de tratamiento (dosis mediana de mitotano al diagnóstico del primer evento adverso de 2g/día). Cuatro pacientes presentaron dos o más eventos adversos. Las toxicidades endócrinas fueron las más frecuentes, presentándose en orden de frecuencia insuficiencia adrenal, hipotiroidismo y dislipemia, que fueron tratados con sustitución hormonal y estatinas respectivamente. La concentración de mitotano en plasma en 3 de 4 pacientes se encontraba por debajo del rango terapéutico.

El tratamiento con mitotano requiere de cuidados individualizados para minimizar los eventos adversos, optimizar los resultados terapéuticos y garantizar la seguridad del paciente.

Palabras clave: carcinoma adrenocortical, mitotano, efectos adversos, neoplasias de la glándula adrenal, insuficiencia adrenal, neoplasias hormono-dependientes

Adrenocortical carcinoma (ACC) is a rare disease (1-2 cases/million population per year) usually diagnosed in the fifth to sixth decade of life, more frequently in women (60%). Clinical presentation includes secretory syndromes (60%) such as hypercortisolism, hyperandrogenism, hyperaldosteronism or overproduction syndromes of more than one hormone. Complete surgical resection is the only curative treatment for these patients[1].

Mitotane is a metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT), widely used for the treatment of ACC. It is a lipophilic molecule, with a concentration 200 times higher in adipose tissue than in plasma. This provides a variable half-life ranging from 18 to 169 days. The therapeutic effect of mitotane is associated with plasma concentrations ranging from 14 to 20 mg/mL.

Therapy with mitotane is indicated as treatment for advanced disease and in the adjuvant setting. Adjuvant treatment is recommended after complete resection for tumors with high to very high risk of recurrence (as established by the Modified risk stratification of recurrence of European Network for the Study of Adrenal Tumors (mENSAT)).

Several adverse events (AEs) related to mitotane have been reported in 30 to 90% of patients[2]. These events are associated with longer duration of treatment and are dose related. In the early stage of treatment, gastrointestinal effects (nausea, vomiting, elevated liver enzymes, hepatitis and diarrhea) and endocrine effects (EAEs) (adrenal insufficiency, hypothyroidism, hypogonadism, hypercholesterolemia) prevail. By contrast, neurological effects are reported in late stages of mitotane therapy, often related to plasma mitotane levels of 20 mg/L or higher[3].

Timely diagnosis and adequate management of AEs may improve adherence and reduce the negative impact in quality of life in patients under treatment. We present a case series in Argentina of toxicities related to mitotane therapy and their management.

Clinical cases

Six patients diagnosed with ACC and treated with mitotane were evaluated. Median age at diagnosis was 46 years [22-62]; four were female. In four cases hormonal overproduction syndromes were diagnosed: 2 of them presented with hypercortisolism/hyperandrogenism syndromes. Four patients were stage II (mENSAT). All patients received mitotane monotherapy during evaluation of side effects. Median time of follow up during mitotane therapy was 13 months [5-36.9] (Table 1).

All patients had AEs related to mitotane. Side effects were detected during the first three months of treatment, with a median dose of mitotane at diagnosis of AE of 2.1 +/- 0.2 gr/day and a median highest dose of 3.25 g/day [2.5-5].

Mitotane blood concentration was obtained in 4 cases, finding only one within the desired range of 14 to 20 mg/mL; the remaining three were below the optimal therapeutic range.

Four patients presented 2 or more AEs. Among them, the most frequent were EAEs in 5 cases, presenting 2 or more endocrine manifestations in each patient (Table 2). Adrenal insufficiency was the more frequent EAEs, followed by hypothyroidism and hypercholesterolemia. One patient presented hypogonadism. Most patients with thyroid dysfunction presented with central hypothyroidism. Treatment of EAEs was hormone replacement (hydrocortisone on day one and levothyroxine as indicated by hormonal workup results). Rosuvastatin was prescribed in cases of hypercholesterolemia. No patient required fludrocortisone replacement.

Three patients evidenced general AEs; 1 showed pruritus (Grade I) at 0.9 months from the onset of mitotane, which was managed with antihistamines with resolution of the symptoms. Another patient developed high levels of liver enzymes (Grade II) after 1.27 months of the beginning of treatment, evolving with rapid progression of non-liver disease and subsequently died. A third patient presented neurotoxicity (Grade III) after 5.4 months of treatment leading to discontinuation of mitotane (this being the only case of mitotane discontinuation due to AE).

At the last visit (median time of follow up 28.1 months [19.5-35]),-one patient continued treatment with mitotane. The remaining five discontinued. In three cases this was due to disease progression, in one due to neurotoxi-

Tabla 1 | General characteristics of patients with adrenocortical carcinoma treated with mitotane

Gender (Female/Male)	4/2
Median age at diagnosis (years)	46 [22-62]
Hormonal secretion	
Hyperandrogenism/Hypercortisolism	2
Nonfunctional	2
Hyperandrogenism	1
Hypercortisolism	1
mENSAT stage	
II	4
IVa	1
IVb	1
Chemotherapy Yes/No	4/2
Indication of mitotane	
Metastatic disease	3
Locally advanced ACC	1
Adjuvant therapy	2

ACC: adrenocortical carcinoma; mENSAT: modified European Network for the Study of Adrenal Tumor

Tabla 2 | Endocrine side effects of patients treated by mitotane

Endocrine side effects	N	Median time from de onset of treatment (months)	Treatment	Observations
Adrenal insufficiency	5	0.8 +/- 0.49	Hydrocortisone	–
Hypothyroidism	4	2.5 +/-1.9	Levothyroxine	Three secondary hypothyroidisms One primary hypothyroidism
Hypercholesterolemia	4	2.2 +/-1.3	Rosuvastatin	Isolated increase of LDL
Hypogonadism	1	1.5	Testosterone	–

city (as previously mentioned) and the other for patient dropout.

Informed consent was obtained from all patients participating in this study.

Discussion

To the best of our knowledge, this is the first documented report of adverse events (AEs) associated with mitotane in Argentina, likely due to the rarity of adrenocortical carcinoma (ACC) and the historically limited availability of mitotane in our clinical practice[4] Of note, since 2025, mitotane has become commercially available in our country.

All the patients in this series were treated exclusively with mitotane during evaluation of side effects, even those with stage IV. These cases have indication of chemotherapy associated with mitotane. However, as mitotane is not readily available in Argentina, there is a delay ranging from 2 to 3 months since its prescription to the actual onset of therapy. Due to this access limitation, ACC patients in stage IV with distant metastasis were treated initially with chemotherapy; they received mitotane therapy in a later stage.

All cases evidenced AEs, which were diagnosed early (during the first three months of

treatment) and while receiving low doses of mitotane (median 2.1 +/- 0.2 g/day), regardless of the achievement of adequate plasma mitotane levels. This result is in agreement with Basile et al. suggesting that mitotane monitoring is more accurate to predict efficacy rather than toxicity. Patients have to be evaluated for AEs from the beginning of treatment[5].

EAEs were the most commonly detected. The frequency of EAEs of the present series is similar to those previously reported[5]. Adrenal insufficiency was present in 5/6 patients of the present series. It is caused by alterations of steroidogenesis and the adrenolytic effects on the adrenal cortex produced by mitotane. Glomerulosa zone is less sensitive to the cytotoxic effect of mitotane than the fasciculata zone, and this could explain the less frequent mineralocorticoid depletion in these patients[2]. Diagnosis of adrenal dysfunction is challenging, as mitotane increases cortisol-binding globulin (CBG), providing inaccurately high or normal levels of plasma cortisol in patients with cortisol depletion. Management comprises hydrocortisone replacement that needs to be initiated on day one of mitotane (doses of 20 mg/day) or after 2 -3 weeks alerting the patient about symptoms[3]. Due probably to the CBG increase and enzymatic metabolic induction of mitotane, corticosteroid replacement requires higher doses of hydrocortisone (50 mg/day or higher) as compared with primary adrenal insufficiency. The optimal dosage of hydrocortisone is largely guided by clinical assessment[3,6,7].

Thyroid dysfunction was found in 4/6 cases, most of them as secondary hypothyroidism. The cause remains unclear; probably, mitotane produces a direct effect on the pituitary gland. Other patients evolved with primary hypothyroidism, with low levels of free thyroxine due to the induction of thyroid hormone metabolism[3,8]. Replacement with levothyroxine is indicated in all cases.

In the present series, more than half of the patients developed hypercholesterolemia, predominantly characterized by an isolated elevation in LDL cholesterol. The pathophysiological mechanism is the upregulation of hydroxymethylglutaryl-CoA reductase by mitotane, which is the rate-limiting enzyme in the biosynthesis of cholesterol[2]. Interestingly, HDL cholesterol levels are also frequently elevated, although the exact mechanism underlying this increase remains incompletely understood. This concomitant rise in HDL cholesterol must be taken into account when determining the need for treatment of hypercholesterolemia. In selected patients, pharmacological intervention may be warranted. Statins, specifically those not metabolized by CYP3A4, such as rosuvastatin and pravastatin, are recommended for managing elevated cholesterol levels[3].

Hypogonadism was observed in one patient. The frequency of hypogonadism varies across reports, with estimates ranging from 30% to 50%. An initial elevation in total serum testosterone may be observed during the first six months of treatment, likely due to an increase in sex hormone-binding globulin (SHBG). Despite this transient rise in total testosterone, free testosterone levels typically decrease, leading to a functional hypogonadal state. Subsequently, a progressive decline in both total and free testosterone concentrations is commonly observed during continued therapy[9]. Mitotane-induced hypogonadism has been associated with deleterious effects on the male reproductive system, including impaired spermatogenesis, decreased libido, and sexual dysfunction[10]. Testosterone supplementation may be considered in patients with low testosterone levels who exhibit symptoms of hypogonadism[3].

No patient referred gastrointestinal side effects. This could be explained by the mitotane scheme indicated in this cohort, starting with a low dose of 1g/day with dose increases after 5 to 7 days. As reported by Terzolo et al, a better tolerance is achieved with stepwise dose increments[6]. On the other hand, all patients received hydrocortisone replacement from the onset of treatment, limiting the symptoms related with adrenal insufficiency.

In conclusion, while mitotane remains an essential treatment modality for ACC, its use demands meticulous clinical management and individualized care to mitigate the risks of AEs, optimize therapeutic outcomes, and ensure patient safety.

Conflict of interest: Maria Laura Iglesias: Advisory board: Celnova Pharma. Sergio Quildrian: Advisory Board: Celnova Pharma. The rest of authors none to declare

References

1. Del Rivero J, Else T, Hallanger-Johnson J, et al. A review of mitotane in the management of adrenocortical cancer. *Oncologist* 2024; 29: 747-60.
2. Bianchini M, Puliani G, Chiefari A, Mormando M, Lauretta R, Appetecchia M. Metabolic and Endocrine Toxicities of Mitotane: A Systematic Review. *Cancers (Basel)* 2021; 13: 5001.
3. Fassnacht M, Dekkers O, Else T, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2018; 179: G1-46.
4. Damilano RA, Bergoglio MT. Adrenocortical carcinoma in women of reproductive age. *Medicina (B Aires)* 2023; 83: 307-10.
5. Basile V, Puglisi S, Calabrese A, et al. Unwanted hormonal and metabolic effects of postoperative adjuvant mitotane treatment for adrenocortical cancer. *Cancers (Basel)* 2020; 12: 2615.
6. Terzolo M, Pia A, Berruti A, et al. Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; 85: 2234-8.
7. Puglisi S, Calabrese A, Basile V, et al. New perspectives for mitotane treatment of adrenocortical carcinoma. *Best Pract Res Clin Endocrinol Metab* 2020; 34: 101415.
8. Russo M, Scollo C, Pellegriti G, et al. Mitotane treatment in patients with adrenocortical cancer causes central hypothyroidism. *Clin Endocrinol* 2016; 84:614-19.
9. Delbarba A, Cosentini D, Facondo P, et al. Androgen serum levels in male patients with adrenocortical carcinoma given mitotane therapy: A single center retrospective longitudinal study. *Front Endocrinol* 2023; 14: 1128061.
10. Innocenti F, Di Persio S, Taggi M, et al. Effect of mitotane on male gonadal function. *Cancers (Basel)* 2023; 15: 3234.