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ADIS DRUG Q&A

Mitotane in adrenocortical carcinoma: a profile of its use

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Abstract

The adrenal cytotoxic agent mitotane (Lysodren®) has a central role in the systemic treatment of adrenocortical carcinoma (ACC), a rare and aggressive cancer of the adrenal glands. Although its precise mechanism of action remains unclear, mitotane has been evaluated and used for more than 60 years and, to date, is the only drug specifically approved for the treatment of ACC. Although ACC continues to be associated with a poor prognosis, mitotane has been shown to provide clinically significant benefit in a good proportion of ACC patients treated with the drug, both in the advanced (unresectable/metastatic) disease and adjuvant therapy settings. While mitotane has generally manageable tolerability with most adverse events (including neurotoxicity) being reversible with dose reduction or treatment interruption, regular monitoring of drug plasma concentrations during treatment is important to help ensure optimal use of mitotane while minimising the impact of drug toxicity.

Plain Language Summary

Adrenocortical carcinoma (ACC), a rare and aggressive cancer of the adrenal glands, is associated with a poor prognosis. Radical surgery remains the only potentially curative treatment; however, in many cases the cancer is only diagnosed in an advanced stage and surgical resection may not be feasible. Furthermore, even with complete surgical resection, disease recurrence is common. Besides surgery, treatment options for ACC remain very limited. Indeed, mitotane (Lysodren®), a derivative of the insecticide DDT, is currently the only drug specifically approved for the treatment of ACC. Mitotane has been shown to provide clinically significant benefit when surgery is not feasible or when used following surgery for the prevention (or delay) of disease recurrence (adjuvant therapy). The side effects of mitotane are generally manageable (and resolve following dose reduction or treatment interruption) although regular monitoring of mitotane concentrations in blood is necessary during treatment to optimise drug effectiveness and safety. In conclusion, mitotane remains the cornerstone of systemic treatment for ACC, both in the unresectable/metastatic disease and adjuvant therapy settings.

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Adis evaluation of mitotane (Lysodren®) in the treatment of adrenocortical carcinoma

An adrenal cytotoxic agent that, to date, is the only drug specifically approved for the treatment of ACC
Recommended (in combination with etoposide, doxorubicin and cisplatin) as first-line treatment for advanced disease
Also has a role in the adjuvant setting and a potential role in the neoadjuvant therapy setting
Adverse events are generally reversible with dose reduction or treatment interruption
Regular monitoring of plasma drug concentrations is necessary during treatment to optimise drug efficacy and safety

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What is the rationale for using mitotane in adrenocortical carcinoma?

Adrenocortical carcinoma (ACC) is a very rare (estimated annual incidence of 0.5–2 cases per million population) and aggressive cancer of the adrenal glands, generally associated with a poor prognosis [1–4]. When feasible, complete surgical resection remains the standard (and only potentially curative) treatment; however, in many cases the cancer is only diagnosed in an advanced stage and surgical resection may not be possible [2, 3, 5]. Furthermore, even with complete resection, recurrence is common [1, 6, 7].

Besides surgery, treatment options for ACC remain limited [1, 3, 5]. To date, the only drug specifically approved for the treatment of ACC is mitotane (Lysodren®), with approval for use in the advanced disease setting (Table 1) [8, 9]. Mitotane (also known as *o*,*p*′-DDD), a derivative of the insecticide DDT, was first examined as a chemotherapy for ACC more than 60 years ago [10] following observations that the oral administration of mitotane to dogs induced a selective necrosis in the adrenal cortex [11]. Although randomised controlled trials involving the use of mitotane in the treatment of ACC remain scarce, based on an accumulation of evidence over several decades, together with the general lack of other effective therapies, mitotane has become the cornerstone of ACC systemic treatment, both in the unresectable/metastatic disease and adjuvant therapy settings [3, 5, 12].

Current European Society of Endocrinology (ESE)/European Network for the Study of Adrenal Tumours (ENSAT) [5], European Society for Medical Oncology (ESMO)/EURACAN (the European Reference Network for all rare adult solid cancers) [3] and National Comprehensive Cancer Network® (NCCN) [12] treatment guidelines all recommend mitotane in combination with etoposide, doxorubicin and cisplatin (EDP) as first-line treatment for advanced/unresectable/metastatic ACC, with mitotane monotherapy also recommended as a first-line option in patients with a low tumour burden. Although the use of mitotane in the adjuvant setting remains off-label [8, 9], on the balance of available evidence, current guidelines also recommend adjuvant mitotane as an option in patients who, after complete surgical resection, have a high risk of disease recurrence [3, 5, 12]. Similarly, mitotane is recommended as an option for consideration in the neoadjuvant setting in patients with stage I–III disease when complete surgical resection is not feasible [3, 5, 12].

How should mitotane be used?

Use of mitotane should involve a suitably experienced specialist [8]. In adults, mitotane treatment should be initiated at a starting dose of 2–6 g/day in two to three [8] (or 3–4 [9]) divided doses, taken orally with a glass of water during meals containing fat-rich food [8, 9]. Taking mitotane with fat-rich food (or milk) enhances drug absorption and may ameliorate potential gastrointestinal (GI) adverse events [8, 13].

A prospective, open-label multicentre 12-week trial was conducted to evaluate two mitotane starting dose regimens in patients with metastatic ACC [14]. Patients in the trial ($n=40$) were assigned to either a low-dose regimen (starting daily dose of 1.0 g escalated to 3.0 g by day 12) or a high-dose regimen (starting daily dose of 1.5 g escalated to 6.0 g by day 4) by the local investigator. Based on the results of the trial, it was suggested that a higher starting dose regimen may be preferable when mitotane is used as monotherapy whereas a lower mitotane starting dose should be considered when used in combination with chemotherapy [14].

Mitotane doses should be progressively increased (e.g. at 2-week intervals) until plasma concentrations reach the target therapeutic window of 14–20 mg/L, or as tolerated [8, 9]. Mitotane plasma concentrations should be assessed after each dose adjustment and at frequent intervals (e.g. 2-weekly, or weekly if a higher starting dose has been used) until the optimal maintenance dose is reached, noting that dose adjustments do not produce immediate changes in mitotane plasma concentrations. In the case of mild toxicity, the mitotane dose should be reduced until the maximum tolerated dose is ascertained. If serious adverse reactions (e.g. neurotoxicity) occur, temporary interruption of mitotane treatment may be necessary until symptoms resolve; 7–10 days after symptoms resolve, mitotane can be restarted at a lower dose. In addition, because of tissue accumulation, regular (e.g. monthly) monitoring of mitotane plasma concentrations should be continued once the maintenance dose has been reached (typically within a 3- to 5-month period). Further regular (e.g. 2-monthly) monitoring is also necessary following interruption of treatment since prolonged mitotane release can occur [8, 9].

Counselling for fertility protection is recommended in females of reproductive age prior to commencing mitotane treatment given that the exact risks of mitotane for the impairment of fertility are unknown [5]. Further information on the use of mitotane is provided in Table 1, including information on its use in special populations (including paediatric patients). Details on potential clinically relevant interactions between mitotane and other drugs or substances are provided in Table 2, as are details on the potential need for high-dose hydrocortisone replacement therapy during mitotane treatment given the accelerated cortisol clearance due to CYP3A4 induction by mitotane [15, 16]. Local prescribing information should be consulted for full details on the use of mitotane in the management of ACC.

Table 1 Summary of the prescribing information of mitotane (Lysodren®) in adrenocortical carcinoma in the EU [8]

What is the approved indication for mitotane?	
Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenocortical carcinoma	
How is mitotane available?	
As 500-mg tablets, for oral use	
How should mitotane be administered?	
Initial dosage	2–6 g/day in 2–3 divided doses
Dosage adjustment	Increase doses incrementally to achieve a blood concentration of 14–20 mg/L, or as tolerated
What are the contraindications to the use of mitotane?	
Hypersensitivity to the active substance or to any of the excipients	
Lactation	
Concomitant use with spironolactone	
How should mitotane be used in special populations?	
Paediatric population	Initiate treatment at 1.5–3.5 g/m^2/day in children and adolescents with the objective of reaching 4 g/m^2/day
	Monitor mitotane plasma concentrations as for adults, with particular attention when plasma concentrations reach 10 mg/L as a quick increase in plasma levels may be observed
Hepatic impairment	Mild to moderate impairment: monitor liver function and exercise caution
	Severe impairment: mitotane use is not recommended
Renal impairment	Mild to moderate impairment: exercise caution
	Severe impairment: mitotane use is not recommended
Older patients (≥ 65 years old)	Exercise caution
Pregnancy	Mitotane can cause foetal harm; give mitotane to pregnant women only if clearly needed and if the clinical benefit clearly outweighs any potential risk to the foetus
Breastfeeding	Breastfeeding is contraindicated during and after discontinuation of treatment for as long as mitotane plasma concentrations are detectable
Females of childbearing potential	Effective contraception must be used during and after discontinuation of treatment as long as mitotane plasma concentrations are detectable
Overweight patients	Exercise caution and closely monitor mitotane plasma concentrations
What other special warnings/precautions pertain to the use of mitotane?	
Before treatment initiation	Surgically remove large metastatic masses as far as possible to minimise the risk of infarction and haemorrhage in the tumour
Adrenal insufficiency	Institute steroid replacement as clinically indicated
	Measure free cortisol and adrenocorticotropic hormone levels to achieve optimal steroid replacement
Shock or severe trauma or infection	Instruct patients to contact their physician immediately if injury, infection, or any other concomitant illness occurs; temporarily discontinue mitotane and administer exogenous steroids
Ovarian macrocysts in premenopausal women	Advise female patients to seek medical care if they experience gynaecological symptoms
CNS toxicity	Perform behavioural and neurological assessments at regular intervals, especially when mitotane plasma concentrations exceed 20 mg/L
Blood and lymphatic system disorders	Monitor red blood cell, white blood cell and platelet counts during mitotane treatment due to a risk of leucopoenia (including neutropenia), anaemia and thrombocytopenia
Bleeding time	Consider the potential for a prolonged bleeding time prior to surgery
Paediatric population	If neuro-psychological retardation is observed during mitotane treatment, investigate thyroid function in order to identify a possible thyroid impairment linked to mitotane treatment

What are the pharmacological properties of mitotane?

Mechanism of action

Mitotane is an adrenal cytotoxic agent; however, its precise biochemical mechanisms of action are not completely understood [8, 9]. The two main biological effects of mitotane are (i) a direct cytotoxic effect on adrenocortical cells and (ii) a decrease in the production of steroids, including cortisol, androgens and dehydroepiandrosterone [15].

In a study in dogs, it was shown that mitotane administration leads to the destruction of the *zona fasciculata* and *zona reticularis* of the adrenal cortex [involved in the synthesis of glucocorticoids (mainly cortisol) and androgens, respectively]; however, there were minimal effects on the *zona glomerulosa* (which is involved in the synthesis of mineralocorticoid hormones, such as aldosterone) [17]. According to a study using human ACC cell lines, the cytotoxic effects of mitotane involve an apoptotic process that is activated following disruption of mitochondria [18]. In further in vitro studies, the sterol-O-acyl transferase 1 (SOAT1) enzyme, an intracellular protein expressed in the endoplasmic reticulum (ER), was identified as a key molecular target of mitotane [19]. The inhibition of SOAT1 by mitotane was found to result in an intracellular accumulation of free cholesterol, oxysterols and fatty acids to toxic levels, leading to ER stress and triggering cell apoptosis [19]. ER stress induced by mitotane also results in the downregulation of the sterol regulatory element binding transcription factor 1 (SREBF1), which leads to reduced transcription of sterol responsive genes and could be one of the mechanisms by which mitotane inhibits steroidogenesis [15, 19, 20].

Mitotane reduces steroid production through its effects on different cytochrome P450 (CYP)-dependent mitochondrial enzymes involved in steroidogenesis both at the transcriptional and functional levels [15]. The ability of mitotane to directly bind some of these CYP enzymes (including CYP11A1 and CYP11B1) may also play a role [15]. Furthermore, the high relative presence of steroidogenic enzymes in the adrenal cortex may (at least partially) explain the enhanced local effect of mitotane in the adrenal glands [15, 20].

Mitotane can also have clinically significant effects on cortisol catabolism [16, 21]. Urinary steroid metabolomics analyses have shown that mitotane treatment is associated with the suppression of 5α- and 20β-reduction and the induction of 1β- and 6-hydroxylation [21]. Furthermore, the strong induction of CYP3A4 by mitotane (Table 2) appears to be associated with accelerated cortisol clearance through greatly enhanced conversion to 6β-hydroxycortisol [16].

Pharmacokinetics

Mitatone has challenging pharmacokinetics overall [22], and several weeks to months of administration are generally required before steady-state concentrations of the drug are reached [14]. Approximately 40% of an oral dose of mitotane is absorbed [9, 23]. The target mitotane plasma concentration (14 mg/L) is usually reached within 3 to 5 months of treatment initiation (median cumulative dose of 363 g) [8]. However, mitotane pharmacokinetics are difficult to predict, with a high level of interpatient variability observed in plasma drug concentrations with different doses [20]. Mitotane is distributed in most tissues in the body but, with its lipophilic nature, tends to primarily accumulate in adipose tissue [8, 9, 24]. Drug metabolism mostly occurs in the liver, although the precise mechanims are unclear [15]. Mitotane can persist in the body for a long time following discontinuation (median plasma terminal half-life = 53 days), again with high interpatient variability (range 18–159 days) [8, 9]. Several factors can potentially contribute to interpatient variability in mitotane pharmacokinetics [20, 22], including individual variability in body composition or body mass index [25], high-density lipoprotein (HDL) cholesterol and triglyceride levels [26], genetic polymorphisms affecting transporter proteins and metabolic enzymes [27–29], and variability in the (auto)induction of metabolic enzymes [25], as well as other as yet undetermined factors [22].

What is the efficacy of mitotane in adrenocortical carcinoma?

In advanced disease

Evidence for the efficacy of mitotane in the treatment of advanced ACC is drawn from a variety of sources, including several key prospective and retrospective studies (Table 3). Across key studies, overall reported response rates ranged from approximately 20–31% for mitotane monotherapy and from approximately 16–49% when mitotane was used in combination with other agents. The variation in response rates between studies likely reflects differences in baseline disease characteristics between different patient populations, differences in response criteria used between studies, and differences in mitotane doses used. Indeed, one of the key findings from early studies was regarding the importance of mitotane plasma concentrations on efficacy outcomes [39–44]. For example, one study involving a consecutive series of 96 patients with ACC, 62 of whom were treated with mitotane at some time during their illness, found that maintenance therapy mitotane serum trough concentrations of ≥ 14 mg/L were associated with significantly prolonged overall survival (OS) from time of diagnosis according to

Table 2 Summary of potential clinically relevant interactions between mitotane and other drugs or substances

Interacting substance(s)	Potential interaction(s)	Action/Management
CYP enzyme substrates (e.g. anticonvulsants, rifabutin, rifampicin, griseofulvin, St. John's wort/*Hypericum perforatum*), particularly CYP3A substrates (e.g. sunitinib, etoposide, midazolam)[a] [8, 9, 15, 16, 30–32]	Mitotane induces CYP enzymes, and thus the plasma concentrations of CYP enzyme substrates may be modified during mitotane treatment	Use caution when co-prescribing mitotane with substances that are CYP substrates
	In particular, mitotane strongly induces CYP3A4, which can result in increased metabolism of co-administered drugs that are substrates of this enzyme	Avoid the concomitant use of mitotane with certain CYP3A4 substrates where minimal concentration changes may lead to therapeutic failure; if concomitant use cannot be avoided, increase the CYP3A substrate dosage in accordance with approved product labelling
	Induction of CYP3A4 by mitotane also causes accelerated cortisol clearance which can lead to adrenal insufficiency necessitating glucocorticoid replacement therapy; CYP3A4 induction has been shown to result in rapid inactivation of > 50% of administered hydrocortisone [16]	Patients receiving mitotane may require high-dose hydrocortisone for effective replacement therapy
Warfarin and coumarin-type anticoagulants [8, 9, 33]	Mitotane can potentially accelerate the metabolism of warfarin through hepatic microsomal enzyme induction	During concomitant use with mitotane, closely monitor patients for a change in anticoagulant dose requirements
Spironolactone [8, 34]	May block the action of mitotane	Concomitant use of mitotane and spironolactone is contraindicated [8]; an alternative therapeutic option to spironolactone should be used
Medicinal products active on CNS [8]	Pharmacodynamic interactions	Consider the potential interaction when co-prescribing medicinal products with CNS depressant action
Fat-rich food [8, 13]	Administration with fat-rich food may enhance mitotane absorption	Mitotane should preferably be taken during meals containing fat-rich food such as milk, chocolate or oil
Hormone-binding proteins [8, 35–38]	Mitotane can lead to increased serum levels of corticosteroid-binding globulin and sex hormone-binding globulin [35, 38]	Measurement of total serum cortisol and testosterone levels may fail to detect hormone deficits
		Increased corticosteroid and testosterone replacement may be necessary to avert adverse events such as adrenal insufficiency and hypogonadism

[a]List of examples is not exhaustive; potential for interaction should be considered for all CYP3A substrates, including oral contraceptives.

univariate ($p < 0.01$) and multivariate ($p = 0.01$) analyses [40]. In the same study, an objective tumour response was observed in 15 (55.6%) of 27 evaluable patients with serum mitotane concentrations ≥ 14 mg/L and in no patients with concentrations < 14 mg/L [40].

According to treatment guidelines for the management of advanced ACC in adults, patients with a low tumour burden and/or more indolent disease may be candidates for mitotane monotherapy [3, 5]. These recommendations are supported by the findings of a large, retrospective, cohort study of 127 patients with advanced ACC treated with mitotane monotherapy at three centres in Germany [42]. In this study, 26 (20.5%) patients achieved an objective response (including three with a complete response), median progression-free survival (PFS) from mitotane initiation was 4.1 months and median OS was 18.5 months. According to a multivariate analysis, a low tumour burden (defined as < 10 tumoural lesions) was associated with improved outcomes [hazard ratio (HR) for progression = 0.51 ($p = 0.002$) and HR for death = 0.59 ($p = 0.017$)]. Improved outcomes were also observed in patients for whom mitotane was initiated at delayed advanced recurrence, suggesting that patients with a long interval between initial diagnosis and the need to start systemic therapy might also be good candidates for mitotane monotherapy [42].

The guideline recommendations for the use of mitotane in combination with EDP as first-line therapy for advanced/metastatic ACC are primarily based on the results of the phase 3 randomised controlled FIRM-ACT trial [45], which found that mitotane plus EDP as first-line therapy was associated with a significantly higher objective response rate (ORR) and significantly longer PFS than mitotane plus streptozocin (Table 3). In the trial, 304 adult patients with advanced ACC not amenable to radical surgical resection were randomised (1:1) to open-label mitotane plus EDP or mitotane plus streptozocin, considered to be the two most successful regimens in patients with advanced ACC disease [45]. Patients with disease progression or unacceptable

toxicity were switched to the alternative regimen as second-line therapy. In the groups randomised to EDP plus mitotane and streptozocin plus mitotane, respectively, two (1.3%) patients and one (0.7%) patient achieved a complete response, 29 (19.2%) and 11 (7.2%) patients achieved a partial response while a further four (2.6%) and two (1.3%) patients achieved disease-free status following surgery after a partial response to study drug treatment. Based on the first-line regimen assignment, no significant between-group difference in OS (primary endpoint) was observed (Table 3), although this result was likely confounded by the permitted cross-over between regimens as well as the fact that mitotane was common to both regimens. The EDP plus mitotane regimen also demonstrated efficacy as second-line therapy, with a PFS of 5.6 months versus 2.0 months for streptozocin plus mitotane in the second-line setting [45].

Further evidence supporting the effectiveness of mitotane in combination with EDP chemotherapy in the treatment of advanced ACC is available from an earlier prospective, single-arm, multicentre phase 2 trial conducted in Italy, in which 72 adult patients were enrolled, most (85%) of whom had undergone previous surgery [46, 47]. In this trial, an ORR of almost 50% was observed (Table 3), which included five patients (6.9%) who achieved a complete response [47]. Ten patients (13.9%) underwent radical surgical resection of residual disease following chemotherapy and became

Table 3 Key studies demonstrating the efficacy of mitotane in advanced adrenocortical carcinoma

Study publication	Treatment (no. of patients)	Key results[a]
Prospective studies		
Haak et al. (1994) [40]	Mitotane (62)	15/27 (55.6%) evaluable patients with mitotane maintenance serum concentrations ≥ 14 mg/L achieved an objective tumour response
		Mitotane maintenance serum concentrations < 14 mg/L had no benefit
Decker et al. (1991) [66]	Mitotane (36)	ORR = 22% (2 CRs)
		DoR = 8.9 months
		OS = 14.5 months in non-responders, 50 months in responders
Baudin et al. (2001) [39]	Mitotane (13)	ORR = 31% (1 CR)
		DoR = 22 months
Fassnacht et al. (2012) [45]	Mitotane + EDP (151) vs mitotane + Sz (153)	ORR: 23.2% (2 CRs) vs 9.2% (1 CR); $p < 0.001$
		PFS: 5.0 months vs 2.1 months; $p < 0.001$
		OS: 14.8 months vs 12.0 months
Berruti et al. (2005) [47]	Mitotane + EDP (72)	ORR = 49% (5 CRs)
		DoR = 18 months
		OS = 28.5 months (47.7 months in responders)
Bukowski et al. (1993) [48]	Mitotane + cisplatin (37)	ORR = 30% (1 CR)
		DoR = 7.9 months
		OS = 11.8 months
Retrospective studies		
Megerle et al. (2018) [42]	Mitotane (127)	ORR = 20.5% (3 CRs)
		PFS = 4.1 months
		OS = 18.5 months
Hermsen et al. (2011) [41]	Mitotane alone (27) or with chemotherapy (64)	ORR = 19% (1 CR)
		OS = 24 months for patients with mitotane plasma concentrations ≥ 14 mg/L ($n = 36$) vs 18 months for patients with mitotane plasma concentrations < 14 mg/L ($n = 55$); $p = 0.04$
Malandrino et al. (2010) [43]	Mitotane + cisplatin-based chemotherapy (55)	ORR = 27.3% (3 CRs)
		OS = 1 year (40.6 months in responders)
Maiter et al. (2016) [44]	Mitotane alone (13) or with chemotherapy (21)	OS = 48 months

CR(s) complete response(s), *DoR* duration of response, *EDP* etoposide, doxorubicin and cisplatin, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *Sz* streptozocin

[a]PFS, OS and DoR data are medians

disease-free. The median OS of the entire cohort was 28.5 months, with androgen hypersecretion being associated with a longer OS and cortisol hypersecretion being associated with a shorter OS [47].

Alternative combination therapy options recommended in guidelines for advanced ACC in patients unsuitable for EDP plus mitotane include etoposide and cisplatin plus mitotane or cisplatin plus mitotane [3, 5]. Cisplatin plus mitotane was evaluated in a phase 2 trial involving 37 patients with advanced ACC where an ORR of 30% was observed (Table 3) [48]. Another phase 2 trial conducted by the same group found that etoposide plus cisplatin had minimal activity in patients ($n = 45$) with advanced ACC (ORR = 11%) [49]. Sixteen patients in this second trial who had had no prior mitotane therapy went on to receive mitotane at disease progression; two (13%) of these patients achieved an objective response [49].

As adjuvant therapy

There remains ongoing debate about the value of mitotane in the adjuvant therapy setting, with the argument for or against its use complicated by the general lack of strong data overall [3, 5]. One study highlighting some of the difficulties of data interpretation was a retrospective study that included 207 patients who underwent resection of ACC (88 of whom received adjuvant mitotane) at 13 institutes in the USA [50]. Although this study found that adjuvant mitotane therapy was associated with decreased recurrence-free survival (RFS) and OS, causality could not be inferred [50]. Indeed, it seems that the group of patients who received adjuvant mitotane was affected by a selection bias towards a higher risk of recurrence which could not be fully adjusted for [3].

The best evidence supporting the use of adjuvant mitotane comes from a multicentre case-control study that compared the outcomes of 47 patients treated at four centres in Italy where adjuvant mitotane was routinely recommended (mitotane group) with 55 patients treated at four other Italian centres where adjuvant strategies were not used (control group 1) [51, 52]. In addition, the study included a second control group involving 75 patients treated at centres in Germany where again patients did not receive adjuvant therapy after surgery (control group 2). Still noting its retrospective nature, the strength of this study comes from its design where, unlike in the US study, patient treatment assignment was determined by the policy of the treating centre rather than patient demographic or disease characteristics, circumventing many potential biases or confounding factors. Baseline features were well balanced between the mitotane group and control group 1, although in control group 2 patients were older and a higher proportion had stage I or II disease relative to the mitotane group [51, 52]. In this study, with a median follow-up of > 10 years, median RFS was significantly ($p < 0.01$) longer among patients in the mitotane group (42 months) than in both control group 1 (17 months) and control group 2 (26 months) [51]. Median OS was significantly ($p = 0.007$) longer in the mitotane group (161 months) than in control group 1 (65 months) but versus control group 2 (92 months) the difference did not reach statistical significance ($p = 0.28$) [51].

More recently, results from the ADIUVO trial, which compared the efficacy of adjuvant mitotane therapy versus observation in ACC patients ($n = 91$) at low to intermediate risk of recurrence following surgery, have become available [53]. ADIUVO is the first randomised controlled trial on adjuvant mitotane in ACC patients. The trial failed to show any significant benefit of adjuvant mitotane in ACC patients at low to intermediate risk of recurrence following surgery with no significant between-group difference in RFS (primary endpoint) or OS [53], although it should be noted that due to difficulties in recruiting sufficient patients (target enrolment of ≈200) the trial remained underpowered. Disease recurrence occurred in 8 of 45 (17.8%) patients in the mitotane group and in 11 of 46 (23.9%) patients in the observation group; there were two and five deaths in the respective groups [53]. Results from a separate cohort of patients ($n = 95$) who were managed in the same way as those in the main study but without randomisation were consistent with the main study findings [53].

As neoadjuvant therapy

Data regarding the use of mitotane as neoadjuvant therapy in patients with ACC remain very limited. However, despite limitations, a single-institute retrospective review of 15 patients with borderline resectable ACC who were treated with neoadjuvant therapy provides some support for the potential value of mitotane in this setting [54]. The 15 patients (median age, 40 years) were categorised as having borderline resectable disease based on anatomic criteria ($n = 6$), metastatic disease ($n = 5$), or marginal performance status or comorbidities precluding immediate surgery ($n = 4$) [54]. Neoadjuvant therapy was administered for a median duration of 4.2 months, with 12 patients receiving mitotane plus chemotherapy, two receiving mitotane alone and one receiving chemotherapy alone. Of the 13 evaluable patients, five had a partial response, seven had stable disease and one had disease progression. Despite advanced disease at presentation (including 40% with stage IV disease), 13 of the 15 patients were able to undergo surgical resection following neoadjuvant therapy, with a median disease-free survival among these 13 patients of 27.6 months [54].

In paediatric patients

Given the particular rarity of ACC in children, evidence relating to the efficacy of mitotane in paediatric patients is more limited than in adult patients [55–57]. Nonetheless, based on available data, the value and role of mitotane in the treatment of paediatric patients with ACC generally appears to parallel that of adult patients despite differences in ACC presenting in childhood versus adulthood. Based on reports from various case series or registries, stage III or IV disease is typically treated with mitotane in combination with cisplatin-based chemotherapy [57–63], with response rates in paediatric patients which appear to be comparable to those in adults [59, 63, 64]. Mitotane (with or without other chemotherapy agents) can also play a role as adjuvant treatment (including for intraoperative tumour spillage) in the paediatric setting [57–59, 61]. Mitotane (together with other chemotherapy agents) has also been used in the paediatric setting as neoadjuvant therapy for inoperable tumours or when complete resection is not possible [57, 58, 61], with some degree of success. For example, in one study, among 11 patients treated with neoadjuvant chemotherapy including mitotane, eight underwent subsequent surgery with complete removal of the tumour possible in five patients [58].

Similar to the treatment of adults, a mitotane plasma concentration of 14–20 mg/L appears to be the optimal therapeutic range [57, 58, 60, 65], although tolerability issues and variability in pharmacokinetics can make this target challenging [58, 64, 65]. There remains debate about the optimal duration of mitotane administration [60], although a treatment period of ≥ 6 months was associated with significantly ($p < 0.001$) improved OS in one study (explorative analysis) [58]. European Cooperative Study Group for Paediatric Rare Tumours/Paediatric Rare Tumours Network - European Registry (EXPeRT/PARTNER) recommendations suggest a mitotane treatment duration in paediatric patients of 1–2 years, depending on tolerance and compliance [57].

What is the tolerability profile of mitotane?

Mitotane has generally manageable tolerability, with most adverse events being reversible with dose modification or drug discontinuation [1, 8, 9, 37]. The most common adverse events relate to GI, nervous system, metabolism or endocrinological disorders [1, 8, 9, 37].

GI adverse events (e.g. nausea, vomiting, diarrhoea, anorexia, mucositis, epigastric discomfort) are the most commonly observed adverse events, occurring in approximately 80% of patients receiving mitotane [8, 9]. GI events generally present early during mitotane treatment, can be managed with supportive care, and are rarely dose limiting [1, 40]. The impact of GI events is reduced by dividing the total daily dose of mitotane into three or four doses and taking the drug with fat-rich food [1, 8, 9].

Approximately 40% of patients receiving mitotane experience adverse events related to neurotoxicity (e.g. sleepiness, vertigo, paresthesia, ataxia, dizziness, headache, mental impairment, polyneuropathy, movement disorder) [8, 9]. In particular, neurotoxicity appears to be associated with higher mitotane doses and longer-term treatment and is frequently the dose-limiting factor during mitotane therapy [1, 8, 9]. Serious CNS adverse events appear to be associated with the cumulative mitotane exposure [8]. Again, neurotoxicity events appear to be reversible after mitotane discontinuation [8, 9].

Most ACC patients receiving mitotane will show signs of adrenal insufficiency (involving multiple mechanisms) [37], and steroid replacement is likely to be necessary [5, 8, 9]. Furthermore, due to increased steroid clearance (with rapid inactivation of > 50% of administered hydrocortisone [16]) together with increased serum levels of corticosteroid-binding globulin (CBG) during mitotane treatment [35, 38], at least twice the standard glucocorticoid replacement dose is usually required [5]. Given the potential for mitotane-induced increases in CBG levels to confound the interpretation of serum cortisol measurements, the combined measurement of plasma adrenocorticotropic hormone levels and 24-h urine free cortisol levels (alongside clinical evaluation) is recommended to achieve optimal dosing of steroid substitution (Table 2) [5, 8]. Even with high-dose glucocorticoid replacement therapy, some patients experience signs and symptoms of insufficient mineralocorticoid activity (e.g. hyperkalaemia, hyponatremia, hypotension, decreased well-being) during treatment with mitotane [5]. In these patients, it is recommended that the addition of fludrocortisone be considered, with decisions based on electrolyte levels, plasma renin level and clinical judgment [5]. A high proportion (≈ 80%) of patients achieve hypothalamic-pituitary-adrenal axis recovery following cessation of mitotane based on a retrospective study of 23 patients treated with adjuvant mitotane for ≥ 2 years, although complete recovery took a mean of 2.7 years from mitotane cessation [67]. In the setting of shock, severe trauma or infection in patients taking mitotane, it is recommended to discontinue mitotane until recovery and to administer hydrocortisone to prevent potential adrenal crisis [8, 9].

Hypothyroidism is another commonly observed adverse event during mitotane treatment, occurring in ≈ 45% of patients treated with the drug [37]. Hypothyroidism in mitotane recipients is generally identified as a reduction in free thyroxine levels, typically occurring after 3–6 months of mitotane treatment. Thyroxine and free thyroxine levels can generally be normalised with 3–6 months of thyroid hormone replacement therapy with levothyroxine [37].

Other endocrinological abnormalities which can occur during treatment with mitotane include increases in sex hormone-binding globulin (SHBG), decreases in blood androstenedione and blood testosterone in females, and decreased blood free testosterone in males [8, 9, 36, 68]. Hypogonadism (with symptoms that can include gynaecomastia, decreased libido and erectile dysfunction) has also been described in male patients receiving mitotane [8, 9, 36, 37]; it is recommended that SHBG, albumin and total testosterone levels be assessed in symptomatic patients every 3–6 months [37]. There have also been several reports of non-malignant ovarian macrocysts occurring in premenopausal women receiving mitotane [36, 68, 69]. The cysts are often bilateral and multiple and can be symptomatic (e.g. associated with pelvic pain or discomfort, or menstrual irregularities) or asymptomatic and detected (e.g. through computed tomography or magnetic resonance imaging) during follow-up [8, 9, 68]. Complications from the cysts (including ovarian torsion and haemorrhagic cyst rupture) requiring surgery have been reported [68]. In some cases, complete regression of the cysts has been observed following mitotane discontinuation [36, 68, 69]. Pelvic ultrasound every 3–6 months has been recommended in premenopausal women receiving mitotane treatment [37].

Dyslipidaemia, most notably hypercholesterolaemia, is also commonly observed during mitotane treatment, occurring in approximately half of patients treated with the drug [36, 37, 70]. Assessment of total cholesterol, HDL cholesterol and triglyceride levels every 3–4 months has been recommended during treatment with mitotane [37]. Dyslipidaemia associated with mitotane treatment can generally be managed with supportive therapies (e.g. statins), although potential drug interactions may need to be considered (Table 2) [36, 37, 70].

Mitotane has also been associated with blood disorders including leucopenia, anaemia and thrombocytopenia [8, 9], and blood counts should be monitored during treatment (Table 1). Furthermore, the potential for prolonged bleeding time, which can also occur during treatment with mitotane [71], should be considered prior to surgery (Table 1). Skin rashes occur in ≈15% of mitotane recipients, although they do not appear to be dose related [8, 9].

Elevations in liver enzymes are commonly observed in patients receiving mitotane, often without clinical significance [1, 8, 9]. However, more serious hepatic adverse events have also been observed, and the potential of mitotane-induced liver damage cannot be excluded [8].

The adverse events profile for mitotane in paediatric patients has a large degree of overlap with that in adults, with GI (e.g. nausea, vomiting, diarrhoea), endocrinological (e.g. adrenal insufficiency, hypogonadism, hypothyroidism) and neurotoxicity (e.g. sleepiness, vertigo, ataxia) adverse events common to both populations [37, 72]. Mitotane has also been associated with effects on physical and hormonal development in paediatric patients and with delays in motor and speech development [72, 73]. Similar to observations in adults, the large majority of mitotane adverse events in children are reversible after dose reduction or drug discontinuation [37, 72].

Further information on specific warnings and precautions pertaining to the use of mitotane is provided in Table 1.

What is the current clinical position of mitotane in adrenocortical carcinoma?

Mitotane remains the cornerstone of systemic treatment for ACC, both in the unresectable/metastatic disease and adjuvant therapy settings. While the overall prognosis for patients with ACC continues to be poor, particularly for those with later-stage disease at diagnosis, in an area where effective treatment options remain very limited, available evidence suggests that mitotane can provide clinically significant benefit in a good proportion of ACC patients treated with the drug. This is reflected in current ESE/ENSAT, ESMO/EURACAN and NCCN treatment guidelines, which all recommend mitotane as a central part of systemic treatment for ACC [3, 5, 12]. For advanced/metastatic ACC, the treatment guidelines recommend the use of mitotane in combination with EDP as first-line therapy [3, 5, 12]. Mitotane monotherapy can also be considered as an option in this setting, with patients with a low tumour burden and/or more indolent disease as particular candidates for monotherapy [3, 5, 12], especially noting the approximately 3- to 5-month period required from mitotane initiation to reach the target plasma concentration [74]. For patients with advanced ACC treated with mitotane monotherapy, it is recommended that EDP chemotherapy be added to the regimen upon disease progression [3, 5]. In the advanced disease setting, mitotane should be continued as long as clinical benefits are observed [8].

Although there is more debate about the value of mitotane as an adjuvant therapy in ACC, on the balance of available evidence, current guidelines recommend the use of adjuvant mitotane in patients who, after complete surgical resection of all macroscopic disease, have a high risk of recurrence (stage III, or R1 resection, or Ki67 > 10%) [3, 5, 12]. In contrast, based on evidence available at the time, the ESE/ENSAT and ESMO/EURACAN guidelines could not suggest for or against adjuvant therapy for patients at low to moderate risk of recurrence (stage I–II, R0 resection and Ki67 ≤ 10%), instead recommending that adjuvant therapy options be discussed on an individual basis [3, 5]. Subsequent to the development of these guidelines, results from the randomised controlled ADIUVO trial have become available, with the trial failing to show any significant benefit of adjuvant mitotane in ACC patients at low to intermediate risk of recurrence following surgery [53]. There is no clear consensus on the optimal duration of mitotane

treatment in the adjuvant therapy setting [5], and treatment times in clinical practice vary [75]. Current ESE/ENSAT guidelines recommend a duration of at least 2 years, assuming acceptable tolerability, but not longer than 5 years (given the low rate of disease recurrence ≥ 5 years post surgery) [5]. Furthermore, accepting some limitations, a multicentre retrospective analysis of 154 patients failed to find evidence of benefit of extending adjuvant mitotane therapy beyond 2 years in patients at low to moderate risk of recurrence, suggesting that exposing such patients to potential drug toxicity for a duration > 2 years may not be justified [75].

Mitotane can also play a role in ACC in the neoadjuvant setting. Current guidelines recommend that if, in patients with stage I–III disease, complete resection is not feasible then neoadjuvant treatment (with mitotane plus cisplatin or EDP, for example) should be considered [3, 5, 12]. Neoadjuvant treatment could also potentially be beneficial in patients for whom tumour shrinkage might permit a more conservative surgical approach [3, 5].

Although based on more limited evidence (given the particular rarity of ACC in children), mitotane has a similar place in the management of ACC in paediatric patients as it does in adult patients, according to current EXPeRT/PARTNER recommendations [57]. While emphasising the importance of the involvement of a multidisciplinary team at diagnosis and during treatment, the EXPeRT/PARTNER recommendations for the treatment of ACC in children and adolescents advise that adjuvant chemotherapy plus mitotane should be considered in the case of incomplete tumour resection or in stage III disease caused by isolated tumour rupture, while either enrolment in a clinical trial or neoadjuvant chemotherapy including mitotane should be considered in patients with primarily inoperable and/or metastatic tumours [57].

While mitotane has been shown to provide clinically significant benefit in a range of settings within ACC disease management, drug toxicity can limit the potential effectiveness in many cases. Although mitotane has generally manageable tolerability, with most adverse events reversible with dose reduction or treatment interruption, mitotane toxicity can present challenges to achieving and maintaining a mitotane plasma concentration within the target therapeutic window of 14–20 mg/L. While there is strong evidence of enhanced clinical benefit at plasma concentrations ≥ 14 mg/L [76, 77], in some patients such concentrations can be difficult to achieve due to tolerability issues. Furthermore, when plasma drug concentrations exceed 20 mg/L there can be an added risk of toxicity (most notably neurotoxicity) without further efficacy gains [8, 9, 39]. The difficulties of achieving and maintaining mitotane plasma concentrations within the target therapeutic window are further complicated by the challenging pharmacokinetics of mitotane, including low intestinal bioavailability, accumulation in and subsequent release from adipose tissue, a very long terminal half-life, substantial interpatient variability, and latency of each dose adjustment to be reflected in plasma mitotane concentrations [15, 20]. These challenges highlight the need for and value of careful regular monitoring of drug plasma concentrations during treatment to help ensure optimal use of mitotane while minimising the impact of drug toxicity in the management of ACC, a rare but aggressive cancer [3, 5, 12].

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