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REVIEW ARTICLE

Management of Endocrine Manifestations and the Use of Mitotane As a Chemotherapeutic Agent for Adrenocortical Carcinoma

Irina Veytsman, Lynnette Nieman, and Tito Fojo

From the Medical Oncology Branch, Center for Cancer Research, National Cancer Institute; and Program in Reproductive and Adult Endocrinology, Bethesda, MD.

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Corresponding author: Tito Fojo, MD, PhD, National Cancer Institute, Bldg 10, Rm 12N226, 9000 Rockville Pike, Bethesda, MD; e-mail: tfojo@helix.nih.gov.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Adrenal cortical carcinoma (ACC) is a rare malignancy in which patients have poor overall 5-year survival. Patients with ACC can present with symptoms of hormone excess, including Cushing's syndrome, virilization, feminization, or—less frequently—hypertension with hypokalemia. In many patients with ACC, advanced disease at presentation precludes surgery or is followed by local relapse or distant metastatic disease that cannot be managed surgically. In these instances, chemotherapy is often tried, but its limited efficacy all too often leaves the problem of persistent hormonal excess. Physicians who treat patients with ACC and severe hypercortisolism should recognize that uncontrolled hormone production is a malignant disease, which has severe consequences that require aggressive management. Because chemotherapy benefits only a small percentage of patients, steroidogenesis inhibitors, including mitotane, ketoconazole, metyrapone, and etomidate, should be used singly or in combination even as chemotherapy is administered. Diligent management with frequent adjustments is required, especially in patients with chemotherapy-refractory tumors that continue to grow. In the absence of randomized, controlled trials, adjuvant use of mitotane remains controversial, although the authors of a recent case-control study argue for its use. Despite difficulty administering effective doses, most clinicians agree that mitotane should be used if the tumor cannot be removed surgically or should be used as adjuvant therapy if there is a high likelihood of recurrence. The option of long-term monotherapy is restricted to patients who tolerate mitotane and either experience a clinical response or are at high risk for recurrence. Recommendations are provided to help manage patients with this difficult disease and to improve the quality of their lives.

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INTRODUCTION

Adrenal cortical carcinoma (ACC) is a rare malignancy, with an incidence of one to two occurrences per 1.7 million of the population.[1,2] ACC has a bimodal distribution, in which there is a higher incidence in children younger than 5 years and in adults in their fourth and fifth decades of life. ACC is slightly more common in women.[2,3] Because ACC is often at an advanced stage at diagnosis, the overall 5-year survival remains between 20% and 45%.[4]

CLINICAL PRESENTATION AND GENETICS

ACCs can be asymptomatic or can present with symptoms of hormone excess or complaints referable to an abdominal mass. Although early studies reported that approximately 50% of ACCs were functional, recent series report hormone secretion in up to 79%—an increase explained entirely or in part by improved assays.[2,3] Classifying ACCs by hormone profile has limited value.[5,6]

Hormone excess presents clinically as Cushing's syndrome, virilization, feminization, or—less frequently—hypertension with hypokalemia (Table 1).[2,7-15] Functional tumors most commonly produce cortisol, which leads to Cushing's syndrome. Compared with other causes of Cushing's syndrome, ACCs cause more virilization, especially in children, because of cosecretion of 17-ketosteroids and dehydroepiandrosterone.[9,10] Although hypertension and hypokalemia may be caused by excess mineralocorticoids, they are more likely caused by markedly elevated cortisol secretion in a patient with ACC. Excess cortisol overwhelms its normal inactivation to cortisone in the proximal tubule by 11β-hydroxysteroid dehydrogenase type 2, which allows cortisol to interact with the mineralocorticoid receptor.[16] In contrast, patients with hormonally inactive ACC usually present with abdominal discomfort or back pain. Only occasionally

Table 1. Clinical and Biochemical Manifestations of Hormone Excess in Adrenal Cortical Carcinoma

Cortisol* (30%-40%)[1-3,5,7,10,11]	Estrogen or Androgen (20%-30%)[1-3,5,8-11]	Mineralocorticoid (rare)[1-3,5,10-15]
Clinical manifestations		
Acne	Estrogens/androgens: Acne, decreased libido, precocious puberty	Hypertension
Decreased growth in children	Estrogens: Feminization in men†‡—gynecomastia, testicular atrophy, and low sperm count	Hypokalemia
Hypertension	Androgens: Virilization in women§—hirsutism, deep voice, male pattern baldness, and oligomenorrhea§	Weakness
Hypokalemia		
Weight gain		
Hormonal manifestations‖		
Elevated 24-hour urinary free cortisol and serum cortisol	Increased serum or plasma estradiol and estrone	Increased 11-deoxycorticosterone and/or corticosterone
Failure to suppress serum cortisol after dexamethasone 1 mg	Increased serum testosterone and adrenal androgens	Increased plasma aldosterone
Elevated late-night salivary cortisol	Increased 24-hour urine 17-ketosteroids (DHEA, DHEAS, D5-androstenediol, D4 androstenedione)	Suppressed plasma renin activity
Suppressed plasma ACTH		Plasma aldosterone-to-renin activity ratio > 20
Increased adrenal androgens (DHEA, DHEAS, D5-androstenediol, D4-androstenedione)		
Increased serum steroid precursors (pregnenolone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, 11-deoxycortisol)		

Abbreviations: ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.
*Also known as Cushing's syndrome.
†Feminization occurs with estrogens and/or androstenedione, which is converted to estrogen peripherally.
‡Effect associated with estrogen excess only.
§Effect associated with androgen excess only.
‖Profile of functional ACC.

do patients present with fever, weight loss, and anorexia. Indeed, the well-being of patients whose tumors do not secrete steroids can be little affected.[17]

Although the cause of most ACC is unknown and most patients lack identifiable risk factors, heredity plays a role in some patients. Risk factors for ACC include the Li-Fraumeni syndrome, multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis coli (Gardner syndrome), and the Beckwith-Wiedemann syndrome. With the exception of the latter syndrome, genetic predisposition is thought to arise from mutations in tumor suppressor genes that increase the risk of several cancers, including ACC (Appendix Table A1, online only). Somatic mutations/alterations in genes responsible for these genetic syndromes also occur in sporadic ACC.

EVALUATION AND WORK-UP

The initial evaluation should determine whether the tumor is functional and should define the extent of disease. The risk of seeding tumor, although not quantified, and the difficulty in the differentiation of benign from malignant tumor argue against a diagnostic biopsy in a patient with an isolated adrenal mass without evidence of metastases; surgical resection is indicated as a diagnostic and therapeutic procedure. However, if widespread metastases argue against surgical resection or if disease elsewhere suggests a primary other than adrenal, a diagnostic procedure is indicated.

Because many patients do not present with symptoms of hormonal excess, it is important to assess hormonal status and the need for steroid replacement to avoid adrenal insufficiency after removing a functioning tumor that suppressed adrenocorticotropic hormone (ACTH) with involution of the contra-lateral adrenal (Table 1). Some studies report hormone secretion, especially cortisol, as an independent, poor prognostic factor, which is an intuitive observation, given cortisol's ability to suppress immune function.[11,18,19] In addition, a recent series identified three factors significantly associated with a shorter survival: older age at diagnosis, stages III (ie, local lymph nodes) to IV (ie, local organ invasion or distant metastases) disease, and cortisol hypersecretion. Abiven et al[20] speculated that the association of cortisol hypersecretion could be attributed to either the comorbidity of Cushing's syndrome, the immunosuppressive effects of excess cortisol, or the "pathophysiology of cortisol-secreting ACC" that leads to the growth of a more aggressive tumor. Importantly, neither mineralocorticoid or androgen secretion nor ortho, para, dichlorodiphenyl dichloroethane; mitotane (Lysodren; Bristol-Myers Squibb, Princeton, NJ) treatment was associated with a risk of metastases.[20] However, another recent study could not discern a significant difference on survival between functional and nonfunctional tumors.[21]

Although both computed tomography (CT) and magnetic resonance imaging (MRI) can be used in the management of patients with ACC, a thin-collimation CT of the chest and abdomen is recommended as the initial imaging technique. Both CT and MRI can help discriminate benign adenomas from malignant lesions. On CT scans, ACCs usually have higher density values (ie, lower lipid content) and are typically inhomogeneous; on MRI, they are usually isointense with liver on T1 images, with intermediate to high intensity on T2 images (Appendix Fig A1, online only).[22-24] MRI, however, is superior in assessing the extent of vascular invasion, especially into the inferior vena cava with right adrenal tumors and should be obtained before a

surgical resection if there is concern regarding vascular involvement.[25] The role of [^{18}F]fluorodeoxyglucose (FDG) –positron emission tomography (PET) is not well established and cannot be recommended in routine evaluation or follow-up.[26-28] Although it might help discriminate a benign adenoma from a malignant tumor, it cannot differentiate ACC from other tumors with high metabolic activities.[29]

Because of the difficulty distinguishing small ACCs (ie, approximately 4 to 6 cm) without local spread or distant metastases from a benign adenoma, several multiparametric approaches have been proposed for establishing malignancy. Among these, the Weiss criteria, first proposed in 1984, is most widely utilized.[30-32] It is based on nine histopathologic properties of adrenocortical tumors known to be malignant either because they metastasized or recurred locally. According to Weiss,[30] a combination of these "nine criteria was most useful in distinguishing malignant from benign tumors": (1) nuclear grades 3 to 4; (2) mitotic rate greater than 5/50 high-power fields; (3) atypical mitoses; (4) tumors with 25% or less clear cells; (5) diffuse architecture; (6) microscopic necrosis; and (7-9) venous, sinusoidal, and capsular invasion. Although Weiss originally noted metastases and/or recurrence in zero of 24 and 18 of 19 tumors with zero to two or four or more criteria, respectively, the threshold for malignancy was subsequently lowered to three or more of the nine histopathologic criteria. Although these properties often cluster and the issue of whether the presence of a greater number of criteria is associated with a worse prognosis is not clear, tumors with higher Weiss scores clinically often behave more aggressively.

TREATMENT

General Considerations

Management of patients with ACC requires a multidisciplinary approach, both at presentation and at disease relapse. At presentation, the principal considerations are surgical, which is the only curative option for ACC and which should be pursued aggressively with a qualified oncologic surgeon. For an adrenal mass that is deemed likely malignant radiologically, laparoscopic resection is contraindicated because of the seeding of tumor than unfortunately occurs. Unfortunately, despite aggressive surgery, 70% to 85% of patients experience relapse locally or develop metastases, which explains a 5-year survival after complete resection of only 16% to 35% and survival for less than 1 year in patients with incomplete resection.[33-35] The latter survival rate argues strongly against a surgical procedure that removes only a part of the tumor, because this can lead to intraoperative seeding and a poor outcome.

Recurrence in the surgical field is common after an optimal resection, and serious consideration should be given to a re-operation, especially if sufficient time—arbitrarily defined as 6 months to a year—have elapsed since the initial operation. Although we believe that repeat surgery may improve survival, the extent of benefit is difficult to discern, because most nonrandomized comparisons encumber no-surgery cohorts with patients who likely had more aggressive disease not amenable to re-operation.[36] Even less clear is the role, if any, of administering radiation to the surgical field. Initial studies[37] reported a lack of benefit with adjuvant radiation, but later studies, which possibly used better techniques, claim high response rates with little toxicity.[38,39] Because of questionable benefit and likelihood that a subsequent re-operation will be technically more difficult, postoperative radiation should only be administered rarely after initial surgery and should be reserved for a select group after a second or subsequent re-operation. Finally, for patients in whom surgery is not possible, chemotherapy is often tried, albeit with only modest success. With the exception of a single regimen that had reported response rates of 54% to 65%,[40,41] the majority of trials report response rates of 13% to 39%, nearly all of which were short-lived, partial responses.[40-47] As regards mitotane early in the disease, the lack of convincing data and the difficulty in administration of most doses argue for its use only if the tumor cannot be removed surgically or as adjuvant therapy only if there is a high likelihood of recurrence. (See Mitotane section).

Both at the outset and especially when tumors grow despite chemotherapy, it is critical to recognize that uncontrolled hormone production by an ACC is a malignant disease with severe consequences. Excess hormone production can impact quality of life and may cause death.[5,48,49] Antihypertensive therapy and deep venous thrombosis prophylaxis should be instituted if clinically indicated. In this Treatment section, we discuss the most commonly used inhibitors of steroidogenesis, provide guidelines for therapy, and consider drug interactions important in patients with cancer. We conclude with general recommendations that integrate various agents.

Mitotane

Background and mechanism of action. Mitotane, or o,p′DDD, is an isomer of the insecticide para (p′) p′DDD and is a chemical congener of the insecticide dichlorodiphenyltrichloroethane. This adrenolytic drug was used first for the treatment of ACC and then was used for other causes of Cushing's syndrome.[50] The development of mitotane dates to the 1960s, when investigators first noted destruction of the zona reticularis and the zona fasciculata in dogs that received mitotane and experienced marked decreases in 17-hydroxycorticosteroids and the glucocorticoid response to ACTH. Subsequent studies demonstrated mitotane inhibition of adrenocortical steroid synthesis by inhibition of cholesterol side-chain cleavage (ie, human cytochrome P450 [CYP], cholesterol desmolase, or 20, 22 desmolase) and 11β-hydroxylase (ie, P450 11β or CYP11b1). This inhibition affects extra-adrenal cortisol disposition by inducing its hepatic clearance, reducing hormone production, and ameliorating the symptoms of hormone excess (Fig 1).[51]

Although not conclusively proven, metabolic transformation and oxidative damage through production of free radicals are generally accepted as the mechanisms that mediate mitotane cytotoxicity, with some transformation occurring in the tumor. Metabolism occurs via a reactive acyl chloride thought to bind adrenal cortical bionucleophiles as well as to serve as the intermediate in the formation of o,p′-DDA (1,1-[o,p′-dichlorodiphenyl] acetic acid). The metabolic reaction is dependent on oxygen and nicotinamide adenine dinucleotide phosphate, and is inhibited by ketoconazole but not by aminoglutethimide, metyrapone, or other steroids. This has led to the suggestion that mitotane is metabolized by a novel, nonsteroidogenic CYP that is active in xenobiotic metabolism in the adrenal cortex.[52] An ex vivo tritium release assay (in which tritiated mitotane is the substrate) has shown a possible correlation between the ability of tumors to metabolize mitotane and the response to mitotane; however, this has not found widespread use.[53]

Treatment recommendations. Mitotane is formulated as 500-mg, scored tablets for oral administration (Table 2). After oral administration, 60% is excreted in stool, usually unchanged, and 40%

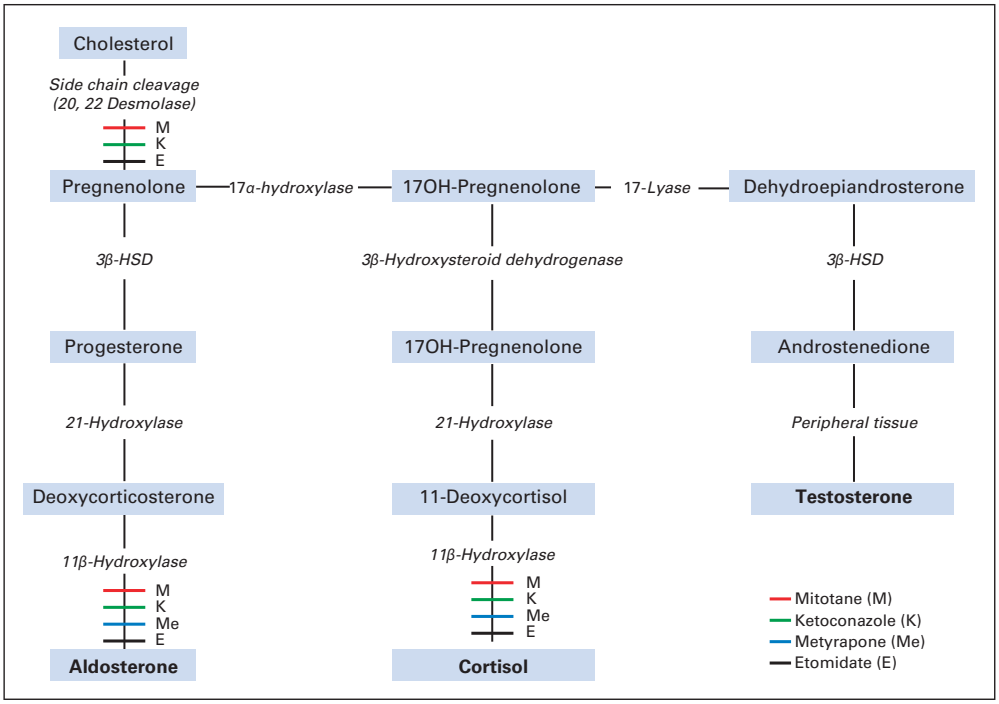

Fig 1. Steroid biosynthetic pathway in the normal human adrenal gland. Enzymes required for steroidogenesis are drug treatment targets.

concentrates in liver, brain, adipose, and adrenal tissues. At initiation of therapy, adipose tissue accumulation delays achievement of therapeutic serum levels for 12 to 14 weeks. Conversely, after discontinuation of mitotane, its slow release from adipose tissue results in measurable serum levels for months.[54-57] Although a rare patient tolerates high doses from the outset, a rapid increase is not possible in the majority of patients. A preferable administration schedule is to start with 1 to 2 g/d and to increase the daily dose by 1 to at most 2 g every 1 to 2 weeks to the maximum-tolerated dose (never $>$ 6 to 10 g/d). Four to six grams is usually sufficient.[58] Mitotane levels should be monitored by using a gas chromatography-flame ionization detection assay initially at 4 to 8 weeks intervals until a level of 10 to 14 mg/L is reached and subsequently at 3-month intervals[59] (Data Supplement: Notes, online only).

As body stores saturate, lower doses are needed. In patients who receive long-term therapy, mitotane doses should be adjusted every 4 to 8 weeks on the basis of serum levels until a stable level on a stable dose is achieved with tolerable adverse effects.

Toxicities and drug interactions. Although mitotane can effectively manage hormone excess, its toxicity profile limits tolerability. GI toxicity, including anorexia, nausea, vomiting, and diarrhea, is reported by 78% of patients who receive daily doses of 2 g or more.[37] At higher doses, neuromuscular manifestations, including ataxia, speech disturbance, confusion, somnolence, muscle tremors, and vertigo, may appear. Rare adverse effects include hyperbilirubinemia, hypercholesterolemia, and a skin rash.[60,61] The latter should be treated symptomatically, because it subsides in most patients. Mitotane increases hepatic production of sex hormone binding globulin and cortisol binding globulin, which factitiously increases total serum levels of gonadal steroids and cortisol. As a result, urinary free cortisol must be used to monitor efficacy. Mitotane can also decrease thyroid hormone, so that thyroid-stimulating hormone and free thyroxine

Table 2. Drugs Used to Manage Hormonal Symptoms in Adrenal Cortical Carcinoma

Drug	Initial Dose	Titration	Maximum Dose	Adverse Effects
Mitotane	1-2 g/d as single or divided dose	1-2 g/d every 1-2 weeks	6-10 g/d with target serum level of 10-14 mg/L	Nausea, vomiting, anorexia, diarrhea, ataxia, speech disturbance, confusion, skin rash, and hyperbilirubinemia
Ketoconazole	200 mg three or four times per day	400 mg/d every 1-2 days	3,600-6,400 mg/d	Nausea, vomiting, abdominal pain, fever, weakness, hypertension, hypothyroidism, gynecomastia, and hypertriglyceridemia
Metyrapone	0.5-1 g/d in two to four divided doses	0.5-1 g/d every few days	4-6 g/d	Hypertension, alopecia, hirsutism, acne, nausea, abdominal discomfort, headache, weakness, and leukopenia
Etomidate*	0.1-0.3 mg/h infusion or 0.2-0.6 mg/kg intravenous bolus	0.1-0.3 over a few hours	3 mg/h†	Hypotension, myoclonus, and sedation

*Propylene glycol vehicle.
†Daily dose of propylene glycol should not exceed 25 mg/kg.

should be monitored every few months, and replacement should be instituted if needed.

Mitotane increases the clearance of exogenously administered steroids so that replacement hydrocortisone doses need to be increased by about one third, from 15 mg in the morning and 7.5 mg in the afternoon to approximately 30 mg daily (ie, 20 mg in morning and 10 mg in afternoon).[62] Higher doses are rarely required, and a decision to administer additional steroids is usually made clinically. Mitotane effects on other drugs are not well documented. For example, full doses of adriamycin, etoposide, and vincristine—chemotherapy agents metabolized principally by CYP3A4—have been administered with mitotane without evidence of more tolerability or additional toxicities.[42] Data that support inhibition of other CYP involvement are limited.[63]

One case report suggests that spironolactone may reduce mitotane efficacy, although the magnitude of the effect is uncertain. Given the lack of convincing evidence, we feel that spironolactone in combination with mitotane is warranted in the management of a patient with hypertension from excess mineralocorticoids.[64]

Ketoconazole

Background and mechanism of action. Ketoconazole is a broad-spectrum antifungal drug with a low toxicity profile that has been in use since the 1970s.[65] The observation that ketoconazole caused gynecomastia was evidence that it could inhibit the synthesis of steroids in mammals.[66,67]

Ketoconazole inhibits C17-20 desmolase, the enzyme responsible for androstenedione biosynthesis, and this can lead to stronger inhibition of testosterone biosynthesis compared with its inhibition of cholesterol side-chain cleavage, 11β-hydroxylation, and 18-hydroxylation.[68-70] In vitro, ketoconazole binds the glucocorticoid receptor directly to prevent ligand binding and stimulation.[71] Ketoconazole inhibition of CYP3A4 occurs at antifungal doses and at the higher cancer treatment doses.[72]

Treatment recommendations. Although an initial ketoconazole dose of 200 mg twice daily is usually recommended for antifungal therapy, patients with ACC and Cushing's syndrome treatment can start with 200 mg three or four times per day (Table 2). The dose can be increased by 400 mg/d every few days while liver function is monitored, and it can reach a maximum of 1,200 to 1,600 mg administered three or four times daily (ie, total daily dose of 3,600 to 6,400 mg). Because ketoconazole requires stomach acidity for absorption, proton pump inhibitors should be avoided.

Toxicities and drug interactions. Occurrences of hepatitis and transient elevations in liver function tests (LFTs; ie, ALT, AST, alkaline phosphatase, bilirubin) have been reported, although death as a result of hepatic dysfunction is rarely reported (one of 10,000 patients).[73] Hepatotoxicity has been observed in patients who received as little as 200 to 800 mg daily. Symptoms begin within 1 to 3 weeks to as late as 12 to 15 months after starting therapy, and this requires continued LFT monitoring. Accompanying symptoms include nausea, backache, fever, and weakness. Withdrawal or reduction of ketoconazole can normalize LFTs within days to weeks.[74]

Other dose-related toxicities that have occurred in more than 40% of patients at ketoconazole doses greater than 800 mg/d include nausea, vomiting, and abdominal pain.[75] Less common adverse effects include hypertension,[76] alopecia,[77] contact dermatitis, an erythema multiforme-like syndrome,[78] adrenal insufficiency,[79] gynecomastia,[80] hypertriglyceridemia,[81] and hypothyroidism.[82]

As a CYP inhibitor, ketoconazole can affect the metabolism of doxorubicin and other anthracyclines, etoposide, the taxanes, and the vinca alkaloids, and it can increase drug toxicity. When using these drugs it is best to avoid coadministration of ketoconazole. However, if ketoconazole is an integral component of the management of hormonal excess, it should be discontinued 24 to 48 hours before giving the chemotherapy drugs listed in Table 3 and may be resumed 24 to 48 hours after the administration of these drugs. Other drugs used in patients with cancer are also affected.[83-85]

Metyrapone

Background and mechanism of action. Metyrapone (also known as metapyrone or metopirone), which was first used in 1959 to assess the pituitary-adrenal axis,[86,87] inhibits adrenal steroidogenesis and is used alone or in combination for Cushing's syndrome as a result of Cushing's disease, ectopic ACTH, or ACC.[88-90] Metyrapone reduces cortisol and aldosterone production by inhibiting 11β-hydroxylation in the adrenal cortex.[91] Because metyrapone inhibits a distal step in the pathway, there is an increase in precursors, including the weak mineralocorticoid 11-deoxycortisol, which obviates the need for long-term mineralocorticoid replacement.[92,93]

The largest series to use metyrapone as a single agent evaluated 91 patients with Cushing's syndrome, including six patients with ACC.[94] In 10 patients with adrenocortical adenomas and in six with ACC, a median metyrapone dose of 1,750 mg/d (range, 750 to 6,000 mg/d) reduced mean cortisol levels to less than 400 nmol/L in 13 patients (81%). Other than causing transient hypoadrenalism and hirsutism, metyrapone was well tolerated.

Treatment recommendations. Metyrapone is available as a 250-mg, soft gelatin capsules (Table 2; Data Supplement: Notes, online only). The dose needed to inhibit cortisol production ranges from 500 to 6,000 mg/d, although little is gained with daily doses greater than 2,000 mg. As with mitotane, metyrapone is begun at a low daily dose of 500 to 1,000 mg (in two to four divided doses) and is escalated every few days.[95]

Toxicities and drug interactions. Adverse effects with metyrapone include hypertension, which caused by excessive secretion of desoxycorticosterone[96,97]; alopecia, hirsutism, and acne, which are most likely secondary to elevated adrenal androgens and testosterone; and abdominal discomfort and nausea.[97,98] Rare adverse effects include bone marrow depression and leukopenia, dizziness, headache, weakness, confusion, and sedation. Drug interactions occur frequently, because metyrapone is a CYP inhibitor. A few occurrences of acetaminophen overdose while on metyrapone have been reported.[99]

Etomidate

Background and mechanism of action. Etomidate, like ketoconazole, is an imidazole derivative that was first marketed as an ultrashort-acting, nonbarbiturate hypnotic that was used in the intensive care unit for rapid hypnosis induction and long-term sedation.[100] However, mortality noted with long-term use uncovered adrenal insufficiency, and this discovery led to use of etomidate in hypercortisolemia.[101]

Table 3. Ketoconazole Interaction With Other Drugs

Drugs Potentiated by Ketoconazole by Degree of Effect				Drugs Contraindicated With Ketoconazole
Major	Moderate	Minor	Synergistic	
Aprepitan	Amlodipine	Armodafinil	Amprenavir	Alprazolam
Fentanyl	Benzodiazepines	Ciclesonide	Darunavir	Astemizole
Irinotecan	Budesonide	Etoposide	Doxorubicin	Cisapride
Lapatinib	Coumarin-like	Mifepristone	Erythromycin	Ergotamine
Levomethadyl	Cyclosporine	Modafinil	Fosamprenavir	
Midazolam	Docetaxel	Phenytoin	Lopinavir	
Simvastatin	Methylprednisone	Vinorelbine	Ritonavir	
Statins	Donepezil			
Sunitinib	Erlotinib			
Temsirolimus	Estrogens			
	Felodipine			
	Fluticasone			
	Gefitinib			
	Imatinib			
	Indinavir			
	Isoniazid			
	Mefloquine			
	Methadone			
	Nifedipine			
	Prednisolone			
	Quinidine			
	Salmeterol			
	Tacrolimus			
	Tretinoin			

Etomidate inhibits the same two enzymes that mitotane inhibits, cholesterol side-chain cleavage and 11β-hydroxylase, and thus impairs cortisol and aldosterone synthesis.[101,102] Inhibition of 11β-hydroxylase occurs at low doses, and impairment of side-chain cleavage occurs at higher doses.[102]

Treatment recommendations. As the only parenteral steroidogenesis inhibitor, etomidate has been used clinically for 2 to 22 weeks in patients in the intensive care unit (Table 2).[103,104] Administration begins as a low-dose infusion of 0.1 to 0.3 mg/h[105,106] or as single-dose boluses of 0.2 to 0.6 mg/kg intravenously.[103] Etomidate can decrease cortisol levels within 11 to 24 hours of initiation of therapy, and dosing should be adjusted to achieve the desired level.[106] To avoid toxicity, the daily dose of the propylene glycol vehicle should not exceed 25 mg/kg.[107] Because of limited clinical experience, the requirement for parenteral administration with daily monitoring, and the occurrence of adverse events, etomidate should be reserved for patients who cannot take oral medications.

Toxicities and drug interactions. At higher doses than those used to inhibit steroidogenesis, etomidate can cause hypotension, myoclonus, and sedation; the addition of other sedating agents may induce hypnosis. Etomidate should be given carefully with calcium channel blockers.[108]

INTEGRATED RECOMMENDATIONS FOR MANAGING HORMONAL SYMPTOMS

Oncologists treating patients with ACC who have severe hypercortisolism should aggressively manage these symptoms in anticipation of a surgical intervention or concurrently with systemic chemotherapy. Because chemotherapy is often inadequate, treatment of the hormonal excess should not be delayed with the expectation that chemotherapy will reduce the tumor burden and improve symptoms. Instead, an aggressive medical approach to the management of excess hormone secretion by using steroidogenesis inhibitors singly or in combination should be adopted, even as chemotherapy is administered. Mitotane, the cornerstone of any strategy, should be started as soon as a diagnosis has been made and should be used in all patients at the highest tolerable dose. Even as mitotane is started, the physician must be aware that a therapeutic level and steady-state level will not be reached for several months, so that other agents must be initiated concurrently, especially if the symptoms are severe. In patients with LFTs within three times the normal levels, we recommend initiation of therapy with ketoconazole to rapidly reduce cortisol production, and we recommend mindfulness of the potential for a pharmacokinetic interaction with chemotherapy agents (Table 3). If LFTs are elevated, if an aggressive ketoconazole dose escalation is unsuccessful in controlling symptoms, or if toxicity develops, metyrapone alone or in combination with ketoconazole can be added. In patients unable to take oral medications, an intravenous infusion or bolus of etomidate can be used with plans to switch to an oral regimen when possible. We would emphasize that physicians must see or speak with these patients once per week, at a minimum, because dose adjustments are often required weekly. Cortisol levels must be monitored frequently to adjust dosage and to avoid adrenal insufficiency, which occurs infrequently in patients with cortisol-producing tumors. Should this occur, hydrocortisone and mineralocorticoid replacement should be instituted as indicated in the Caveats Regarding the Use and Monitoring of Steroidogenesis Inhibitors section.

We note here that, in a patient with advanced ACC and an anticipated short life span, the physician could consider a palliative approach that emphasizes the benefit of managing Cushing-related symptoms while avoiding the adverse effects of chemotherapy. Mitotane in this setting could effect a reduction in tumor; however, given its limited activity as a cytotoxic agent in patients with advanced disease, this should not be expected by either the patient or the caregivers.

Caveats Regarding the Use and Monitoring of Steroidogenesis Inhibitors

All adrenal steroidogenesis inhibitors can cause adrenal insufficiency. It can be difficult to distinguish between adrenal insufficiency and drug toxicity, and the physician must often rely on clinical intuition to ascertain the adequacy of adrenal function.

Although control of hormone production may not be possible in most patients with rapid tumor growth, an aggressive management occasionally is successful in achieving partial or—rarely—complete inhibition of hormone production. In patients receiving mitotane, serum cortisol cannot be used to monitor treatment efficacy, because it increases cortisol-binding globulin and artificially raises total cortisol. These patients should be monitored by using urinary free cortisol (Data Supplement: Notes, online only).[98] If it is possible to block cortisol synthesis, patients should receive replacement therapy. Many physicians prefer this option so as to avoid the risk of adrenal insufficiency (and death). Hydrocortisone (20 mg in the morning and 10 mg in the afternoon) and fludrocortisone (100 to 200 μg in the morning) should be administered, and the patient should be advised to obtain a bracelet or necklace that will alert emergency personnel to the possibility of adrenal insufficiency in the case of an acute emergency. Finally, we would note that, when mitotane is used as an antitumor agent in a patient without evidence of hormonal excess, replacement therapy must be instituted at the outset or within the first few months of starting mitotane, because its adrenolytic properties reduce normal adrenal hormone production.

MITOTANE AS AN ANTITUMOR AGENT: ISSUES AND CONTROVERSIES

Because mitotane has both antitumor and antihormonal properties, we discuss here the use of mitotane as an antitumor agent. Unfortunately, the rarity of ACC has precluded conduct of studies needed to answer many questions (Data Supplement, online only).

Single-Agent Mitotane

Mitotane (Table 4) was initially used as monotherapy in patients with locally advanced or metastatic ACC; tumor regression was reported in 34% to 61% of patients with measurable disease, and a reduction in urine hormone levels of 69% to 85% was reported (Table 4).[109-111] Unfortunately, the high response rates in these early studies have not been supported by subsequent trials, and it appears that partial response occurs in, at most, 10% to 30% of patients and likely

Table 4. Mitotane As Monotherapy

Study	No. of Patients	Response Type		Patients Who Responded (%)	Comment
		CR	PR		
Bergenstal et al[109]*	18	—	7	39	Evaluated by x-ray and steroid response
Hutter et al[110]*	59 with measurable disease	—	20	34	Evaluated by x-ray and/or physical exam
Hutter et al[110]*	62 with measurable steroid secretion	—	43	69	Evaluated by corticosteroid response
Lubitz et al[111]*	75 with measurable disease	—	46	61	Evaluated by x-ray and/or physical exam
Lubitz et al[111]*	61 with measurable steroid secretion	—	52	85	Evaluated by steroid response
Venkatesh et al[112]†	72	—	21	29	—
Luton et al[11]‡	37	—	8	22	Mitotane did not have a significant effect on survival
Decker et al[113]§‖	36	2	6	22	Poorly differentiated tumors excluded; adriamycin treatment
Haak et al[114]¶	55	8	7	27	Responses were observed only in patients with levels > 14 mg/L
Barzon et al[115]¶	11	—	2	18	—
Williamson et al[44]§#	16	—	2	13	Only patients without benefit from cisplatin/etoposide were treated
Baudin et al[57]§¶	13	1	3	31	Responses were observed only in patients with levels > 14 mg/L

Abbreviations: CR, complete response; PR, partial response.
*Early studies used chest x-ray for evaluation of metastatic lesions. CR was defined as disappearance of all evidence of tumor, and PR was defined as a diminution in size of the tumor. Steroid response was good if a decrease in urinary excretion > 50% was recorded; was moderate if a decrease of 30% to 50% was reported; and was poor if a < 30% decrease was reported.
†Treatment was defined as moderately effective if the tumor decreased in size but survival was less than 2 years, or if stable disease for greater than 2 years was achieved, and it was defined as very effective if a decrease in tumor size was associated with survival for more than 2 years or if metastases were stable for more than 3 years; in this table, responses are given as PR.
‡PR was defined as a ≥ 10% regression of the area of at least one measurable tumor deposit.
§In latter studies, CR was defined as the disappearance of all tumor.
‖PR was defined as a ≥ 50% decrease in the sum of the cross-sectional areas of all lesions with no progression in any lesion.
¶WHO criteria, as follows, were used: PR was defined as at least a 50% decrease in the sum of the products of the longest diameter of the greatest perpendicular dimensions of all measurable lesions for at least 1 month without the appearance of new lesions.
#PR was defined as ≥ 50% decrease in the sum of the products of the perpendicular dimensions of all measurable lesions on at least two evaluations.

Table 5. Adjuvant Mitotane

Study	Mitotane			Control			Study Results
		Survival (months)			Survival (months)		
	No. of Patients	DFS	OS	No. of Patients	DFS	OS	
Pommier et al[34]	7	29	NR	43	30	NR	Negative
Vassilopoulou-Sellin et al[117]	8	10	14	6	23	34	Negative
Haak et al[114]	11	NR	51	15	NR	61	Negative
Barzon et al[115]	7	8	24	11	13	54	Negative
Dickstein et al[118]	6	≥ 46	≥ 46	—	—	—	Positive*
Baudin et al[57]	11	7	24	—	—	—	Negative*
Terzolo et al, group 1[21]†	—	—	—	55	10	52	Positive
Terzolo et al, group 2[21]†	47	42	110	75	25	67	

Abbreviations: DFS, disease-free survival; OS, overall survival; NR not reported.
*Results found with small sample size and lack of control arm.
†Group 1 control group was from centers in Italy; Group 2 control group was from centers in Germany.

much less than this.[4,11,57,112-116] The discrepancies may be explained in part by more accurate imaging modalities in later studies and by the possibility that, in early studies, assessment of efficacy was influenced by the effect of mitotane on steroid production and clinical symptoms, which can occur without tumor reduction. These discrepancies aside, mitotane has measurable activity in ACC and should be considered as a single agent or in combination in the therapy of disease that cannot be surgically removed. Although the extent of tumor reduction may not be great, most clinicians with experience using mitotane believe it slows tumor progression and advocate its continued use in patients who have shrinking or stable disease and who are tolerating therapy well. Two small studies demonstrated measurable antitumor activity only with serum mitotane levels greater than 10 to 14 mg/L.[57,114] Consequently an attempt should be made to achieve these levels, even if done gradually over several months. However, if the clinical impression is of benefit, even if serum levels are less than 10 mg/L, therapy should be continued, because these small studies only examined correlations with response to therapy, not time to progression or other outcomes; this examination precludes the conclusion that lower doses have no value in delaying growth. Especially in patients with a more indolent disease course, the clinician's assessment of benefit should guide the decision on whether to continue therapy.

Mitotane in the Adjuvant Setting

Even less clear is whether mitotane should be used after surgical resection, in an adjuvant setting (Table 5).[33-35] Initial studies reported improved survival with mitotane.[112,119] However, several subsequent studies failed to demonstrate a survival benefit for mitotane[11,114,115] or suggested a negative effect.[34,114,117] A more recent analysis compared the outcome in 47 patients treated with adjuvant mitotane therapy with that of two control groups. Surprisingly, more tolerable mitotane doses of 2 to 3 g/d demonstrated significant benefit in the adjuvant setting.[21,120] However, the results of this retrospective nonrandomized study must be viewed cautiously, especially since the advantage was confined to time to recurrence but not to overall survival, although one cannot exclude the possibility that a longer duration of administration might have had even greater benefit. The lack of convincing evidence and the difficulty administering therapeutic doses (see Length of Mitotane Administration and online-only Appendix) have often guided the following two recommendations: (1) Adjuvant mitotane therapy should be used only in patients with a high likelihood of recurrence (ie, in patients who have large tumors with many of the features that comprise the Weiss score; see Evaluation and Work Up)[30-32] and small or questionable surgical margins. (2) Mitotane should be used early in the course of therapy for instances in which the tumor cannot be fully removed surgically.[31] Until additional data are available, we would continue to counsel such an approach.

Length of Mitotane Administration

Long-term mitotane monotherapy should be given only to patients who tolerate it well and who experience a clinical response or to those who are at high risk for recurrence. The optimal duration of therapy in such patients is not known. A recommendation of indefinite is most conservative and may be possible in a patient who has tolerated therapy well. Continuation of a difficult therapy for a prolonged period of time is possible, because months of therapy finally saturate body stores, which reduces the maintenance dose and improves tolerability. However, suboptimal therapy (judged by serum mitotane levels) limited by adverse effects should not be continued, because there is little chance of benefit in the face of continued toxicity. Although suboptimal therapy cannot be accurately defined—levels of 10 to 14 mg/L are often cited as optimal on the basis of the two small studies cited in the Single-Agent Mitotane section—lower doses are likely of some value, because tumor shrinkage or stable disease can occur with levels in the 5 to 10 mg/L range, a clinical observation also noted in the recent retrospective analysis.[21]

In conclusion, oncologists who treat patients with ACC will find that not only is reducing the tumor burden difficult, but so too is the deceptively easier goal of achieving eucortisolism; full symptom control cannot be achieved in many patients. The rapidly changing clinical presentation in a patient with progressive disease may require frequent dose adjustments to achieve optimal control of hormone excess. This palliative care is designed to reduce morbidity and to improve the quality of life, both important goals in patients with ACC as in patients with other cancers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Irina Veytsman, Lynnette Nieman, Antonio Tito Fojo
Collection and assembly of data: Irina Veytsman, Antonio Tito Fojo
Data analysis and interpretation: Irina Veytsman, Lynnette Nieman, Antonio Tito Fojo
Manuscript writing: Irina Veytsman, Lynnette Nieman, Antonio Tito Fojo
Final approval of manuscript: Irina Veytsman, Lynnette Nieman, Antonio Tito Fojo

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