

MEDICAL MANAGEMENT OF ADRENAL DISEASE: A NARRATIVE REVIEW

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Adrenal diseases comprise for a variety of medical endocrine issues, ranging from partial or complete gland insufficiency, to several kinds of adrenal hyperfunction, either of congenital or neoplastic etiology.

For hypofunction of the adrenals (partial or complete) the treatment of choice is medical; the mainstay of treatment is hydrocortisone. Patients with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency are treated with glucocorticoids to control androgen excess. Most benign neoplastic adrenal diseases that cause hyperfunction of the gland are surgically treated, however this may not be always feasible or effective. For Cushing's syndrome ketoconazole controls cortisol's hypersecretion, whereas in case of bilateral idiopathic hyperaldosteronism spironolactone controls hypokalemia and hypertension. For neoplastic adrenomedullary disease surgery is the treatment of choice; medical treatment is used preoperatively (mainly alpha blockers) and in case of disease persistence and /or recurrence (mainly metyrosine). For malignant adrenocortical disease, surgical removal remains the indicated treatment, but if the potential for surgical intervention is limited due to tumor extension, medical treatment can alleviate symptoms of hormone hypersecretion; mitotane in selected patients has good results.

Key words: Adrenal Gland – Adrenocortical Hyperfunction – Cushing's syndrome – Hyperaldosteronism – Congenital adrenal hyperplasia – Adrenal insufficiency – Pheochromocytoma – Adrenal cancer – Drug therapy

For most non-neoplastic adrenocortical disease medical therapy is the treatment of choice, usually with steroids. For neoplastic adrenomedullary or adrenocortical disease surgery is the treatment of choice; medical treatment is used pre- and postoperatively (in case of disease persistence and /or recurrence). Most current clinical trials for medical treatment of adrenal diseases focus on neoplastic diseases.

Adrenal insufficiency

Adrenal insufficiency can be either primary or secondary to inadequate corticotropin (ACTH) stimulation.

Patients with proven or suspected adrenal insufficiency or suppression should be treated with supplemental doses of hydrocortisone or of an equivalent glucocorticoid (MIEURE et al. 2007).

Primary adrenal insufficiency. Patients should receive adequate hormone replacement (MIEURE et al. 2007) to correct lack of both glucocorticoid and mineralocorticoid but care should be taken not to "overshoot" therapeutic levels. The mainstay of treatment is hydrocortisone (which is transformed by CYP11B1 to active cortisol). Adult dosing is actually proportional to patient body weight and is usually 20-30 mg/day, whereas for children dosing is 10-20

mg/m²/d. To mimic natural diurnal adrenal rhythm, two thirds of the daily dose are usually given in the morning and one third in late afternoon. Since cortisol may potentially harm the gastrointestinal tract, patients are advised to take the drug with meals, milk or an antacid. Side effects include gastritis, insomnia or irritability, whereas overdose may accentuate preexisting diseases, including diabetes mellitus, hypertension or psychosis. Another adrenal product that has to be replaced is mineralocorticoid; usually fludrocortizone at 0.05-0.10 mg/day is given per os, with concomitant dietary salt intake (3-4 g/day). Side effects include hypokalemia, hypertension or congestive heart failure caused by sodium retention. As with the normal response of adrenals to any stressful situation, hydrocortisone replacement should be adjusted to such conditions. In case of fever, infection or other intercurrent illness, the dose of hydrocortisone should be doubled. In severe illness, it has to be increased to 75-150 mg/day (COOPER and STEWART 2003). For surgery, cortisone has to be supplemented intravenously either continuously at 10 mg/hour or 50-100 mg every 8 hours, for the day of surgery and the first to second postoperative days, then gradually tapered over 1 to 2 days, returned afterwards to supplementation by mouth (MIEURE et al. 2007). If the daily hydrocortisone given exceeds 100 mg/day, no mineralocorticoid supplement is needed (higher-dose cortisone has sufficient mineralocorticoid effects).

The treatment of subtle or relative adrenal insufficiency that is often observed in critically ill patients is controversial, particularly after the recent disappointing results of the CORTICUS trial. Hydrocortisone may nevertheless be of use in patients with septic shock that remain vasopressor-unresponsive (SPRUNG et al. 2008).

Secondary adrenal insufficiency. The goal of treatment in secondary insufficiency is replacement of the missing hormones, if no cure can be achieved at the level of the hypothalamus or pituitary. When gradual down-regulation of the hypothalamic-pituitary-adrenal axis has been provoked by exogenous glucocorticoids, gradual discontinuation of the steroids is the treatment of choice. There are no universally accepted guidelines for tapering off steroids.

In female patients with primary adrenal insufficiency, replacement with androgens is advised by some experts. In particular, various regimens of dehydroepiandrosterone (DHEA; given at 25-50 mg per os) seem to improve sense of well being as well as bone mineral density (MUNVER and VOLFSOON 2006). However, although age-

related decline in adrenal secretion of DHEA or its sulfate (DHEAS) is well documented, the indiscriminate replacement with either DHEA or DHEAS in older individuals is controversial (relevant studies with daily doses of 50 to 100 mg have yielded overall equivocal results in well-being or libido) (MORALES et al. 1998; ARLT 2006).

Acute adrenal insufficiency. An – almost – definitive diagnosis of acute adrenal insufficiency is obtained with an adrenocorticotrophic hormone stimulation test. Emergency management of hypoadrenocorticism includes recognition and treatment of life-threatening arrhythmias, replacement of intravascular volume to normalize perfusion, correction of electrolyte abnormalities and of hypoglycemia and administration of glucocorticoids. Normal saline (0.9% w/v) is the infusion of choice, since half-normal saline (0.45% w/v) may worsen hyponatremia. One hundred mg of hydrocortisone should be administered as an intravenous bolus, followed by hydrocortisone at rate of 10 mg/hour (approximately 250-300 mg/day) for 2-3 days. Alternatively, dexamethasone can be given as a 4 mg bolus intravenously (to avoid interference with cortisol assays) (MIEURE et al. 2007). After recovery, doses are tapered and supplementation is switched to tablet form.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) encompasses inborn autosomally recessive deficiencies in adrenal steroidogenesis enzymes (most often of 21-hydroxylase) resulting in the relative inability of the adrenals to synthesize cortisol (CLAYTON et al. 2002). The salt-wasting form of CAH (presenting with a primary metabolic crisis regardless of gender in the first weeks of life) can become life-threatening. Less severe forms are the simple virilizing (presenting with hypertrophy of the clitoris – only in girls) and the non-classical form (usually diagnosed in girls with polycystic ovary syndrome phenotype around the onset of puberty) (MERKE and BORNSTEIN 2005).

Glucocorticoid replacement. Patients with classic 21-hydroxylase deficiency and nonclassic symptomatic CAH are treated with glucocorticoids (WHITE and SPEISER 2000), thus suppressing excessive secretion of corticotropin releasing hormone (CRH) and ACTH and lowering adrenal androgen levels. In children 10-20 mg/m²/day of hydrocortisone are given in 2 or 3 divided doses (physiological levels are 6-7 mg/m²/day) (WHITE and SPEISER 2002). Hydrocortisone has a short half-life

Table 1
Comparison of glucocorticoids

Steroid (administration)	Biological half-life (hours)	Normal daily equivalent (with hydrocortisone as baseline; mg)
Hydrocortisone (intravenous or per os)	8-12	20
Prednisolone (intravenous or per os)	18-24	5
Prednisone (per os)	18-36	5
Methylprednisolone sodium succinate (intravenous)	18-36	4
Dexamethasone (intravenous or per os)	36-72	0.5-0.75

(of approximately 8-12 hours) and its use may minimize growth suppression (thus it is preferable for children), in comparison to long-acting prednisone and dexamethasone, but necessitates at least 2 doses daily (ROSS and ROSTAMI-HODJEGAN 2005). Adults can be treated with prednisone (5.0-7.5 mg/day divided in 2 doses) or dexamethasone (0.25-0.5 mg in 1 or 2 daily doses), usually taking care not to exceed the equivalent of 20 mg hydrocortisone/m²/day (Table 1). Experience in the management of CAH from the National Institutes of Health (USA) and elsewhere has shown that adrenal androgens' secretion is better controlled by administering the largest glucocorticoid dose at bedtime (thus suppressing nighttime ACTH secretion) (MERKE 2008). Patients should be regularly evaluated for efficacy of treatment, by assessing 17-OH progesterone (keeping it within a range of 100-1000 ng/dL) and androstenedione levels and testosterone levels in females and prepubertal males (WHITE and SPEISER 2000). Children should undergo an annual bone age x-ray and monitoring of linear growth. Adverse effects of treatment are growth suppression (ROSS and ROSTAMI-HODJEGAN 2005) or iatrogenic Cushing's syndrome in response to higher than necessary doses of steroids. In case of illness or stress steroid dosage has to be increased (tripled in minor illness, and administered intramuscularly as hydrocortisone succinate).

Patients with non-classic CAH should be treated when they manifest symptoms of androgen excess and particularly in children with precocious pubarche, or girls with hirsutism, oligomenorrhea and acne. Infertility in both sexes and low sperm counts in men are additional treatment indicators (ARLT and KRONE 2007; MERKE 2008).

In pregnant women with fetuses at risk for CAH, prenatal maternal therapy with dexamethasone is given at 20 microg/kg/day, based on pre-pregnancy weight to a maximum of 1.5 mg daily in 3 divided doses, begin-

ning before the 7th to 8th week of gestation (WHITE and SPEISER 2000; NIMKARN and NEW, 2009). Treatment is continued only for female fetuses (the caveat is that only in 1 of 8 fetuses need dexamethasone at such an early stage of life *in utero*).

Mineralocorticoid replacement. Apart from glucocorticoid treatment, children suffering from the salt-wasting form of 21 hydroxylase deficiency also need mineralocorticoid (fludrocortisone 0.1-0.2 up to 0.4 mg daily) and sodium chloride supplements (1-2 g daily). Fludrocortisone levels may be decreased after early infancy. Plasma renin activity (PRA) is used to monitor mineralocorticoid and sodium replacement (suppressed PRA levels indicate overtreatment) (BIGLIERI and KATER 1991).

Perspectives in the therapy of congenital adrenal hyperplasia. A novel four-drug regimen for CAH is under clinical trials: flutamide (an androgen-receptor blocker) and testolactone (an aromatase inhibitor) are co-administered with low-dose hydrocortisone and fludrocortisone in children suffering from CAH. In experimental studies, children were given carbenoxolone (an inhibitor of 11-beta hydroxysteroid dehydrogenase, 11-HSD) and hydrocortisone (WHITE and SPEISER 2000). Inhibition of the oxidative 11-HSD reaction provides the body with higher endogenous active cortisol, thus lowering the need for suppression. In another study of only two adults with concurrent malignancies, chlormadinone acetate (an antiandrogen used for prostate cancer) was given with hydrocortisone, resulting in normalization of adrenal androgens and ACTH (KAGEYAMA et al. 1995). Bilateral adrenalectomy with life-long steroid coverage can be an alternative to suppressive glucocorticoid treatment; controlling adrenal insufficiency is easier than regulating excess steroid production (VAN WYK et al. 1996). Gene therapy for CAH, although contemplated (GOTOH et al. 1994), has

not been attempted in humans yet and prospects are not very promising thus far.

Cushing's syndrome

Cushing's syndrome results from hypercortisolism caused by pituitary hypersecretion of ACTH (Cushing's disease; 80 % of cases), adrenal adenomas/carcinomas (10% of cases) and ectopic ACTH secretion of neoplastic origin (10 % of cases) (NIEMAN and ILIAS 2005).

The treatment of choice for Cushing's is surgical excision of the causative tumor. Medical treatment is reserved for patients that cannot be operated (DIEZ and IGLESIAS 2007), to inhibit steroidogenesis in severely cushingoid subjects (if possible preoperatively or for subjects with unknown-"occult" sources of ACTH hypersecretion) and post-radiation therapy (since the latter's effect becomes more pronounced over time), for patients with persistent or recurrent Cushing's after surgery (NEWELL-PRICE et al. 2006).

Centrally-acting agents for Cushing's disease.

Compounds that affect CRH or ACTH synthesis or release are rarely – if ever – used for Cushing's disease. They include cyproheptidine, bromocriptine, somatostatin and valproic acid. Cyproheptidine has anticholinergic, antihistaminic and antiserotonergic activity; with an average dose of 24 g it decreases CRH and ACTH. Alternative agents include metergoline, ritanserin or ketanserin. Valproic acid promotes gamma-aminobutyric acid (GABA) secretion, which in turn inhibits CRH release; average dose is 1-2 g/day (DIEZ and IGLESIAS 2007). Octreotide is a somatostatin agonist that has proven beneficial only in vitro. Dopamine-agonists (primarily bromocriptine) have proved of limited efficacy and recurrence of Cushing's disease ensues after their discontinuation (DIEZ and IGLESIAS 2007).

Agents that inhibit steroidogenesis. Ketoconazole, mitotane (o, p-DDD), trilostane, metyrapone, aminoglutethimide and etomidate decrease cortisol production by directly inhibiting steroidogenesis at one or more enzymatic steps (NIEMAN and ILIAS 2005). According to the dosage steroidogenesis' blockade may be either complete (with the need for additional exogenous glucocorticoids) or partial. The efficacy of steroidogenesis inhibitors is limited and their dosage must be increased since the gradually lower cortisol levels provoke ACTH hypersecretion, which in turn, stimulates cortisol production in the adrenals (ARNALDI et al. 2003). Patients rarely remain in remission after discontinuation of treatment (NIEMAN and ILIAS 2005). Ketoconazole is an imi-

dazole derivative that inhibits steroidogenesis by acting on P450 enzymes in the adrenals. It is started at 400-600 mg/day and increased every 3 days to 1600 mg/day in four divided doses. Ketoconazole is commonly used because of its effectiveness as monotherapy and favorable side-effect profile. Common side-effects include gynecomastia and serum aminotransferase elevation in 5%-10% of patients, while serious hepatic impairment occurs in 1 out of 15000 users (NIEMAN and ILIAS 2005). Ketoconazole needs gastric acid to be metabolized, thus it is not an option for patients with achlorhydria or proton pump inhibitor users. Mitotane inhibits mainly side-chain cleavage in steroidogenesis. Mitotane therapy begins at 0.5-1.0 g/day and is increased gradually in 0.5-1.0 g increments every 1 to 4 weeks up to 2-3 g/day; the therapeutic effect is gradual and may take weeks to be evident. Mitotane has significant gastrointestinal (nausea, diarrhea), neurological (dizziness, vertigo, confusion) and metabolic (hyperlipidemia) side-effects. Adrenal insufficiency is a rare complication; in such occurrence mitotane should be discontinued for 1 week and then the patient's condition should be reevaluated (NIEMAN 2002). It is totally contraindicated in women willing to become pregnant, as it is teratogenic. Trilostane is a relatively weak inhibitor of steroidogenesis. Maximal dose is 1.4 gr daily (DEWIS et al. 1983). Metyrapone, given at 2 to 3 g/d, may also be effective, either alone or in combination with other steroidogenesis inhibitors or with radiotherapy. Dosage begins at 0.5-1.0 g/day and is increased every few days up to 6 g/day. Side-effects include hypertension, acne and hirsutism, as androgenic precursors increase due to the inhibition of 11-HSD. Aminoglutethimide, another steroid synthesis blocker, is used at a dose of up to 1 g/day. It is effective in combination with metyrapone. Neurological side-effects, as blurred vision, sedation, dizziness, depression, may occur. Etomidate is an intravenous anesthetic derivative of imidazole that inhibits steroidogenesis even when it is given at non-sedating doses (SCHULTE et al. 1990) . It has been used in rare cases of hypercortisolemia that was unresponsive to other agents (KRAKOFF et al. 2001).

Agents that block cortisol's action. Mifepristone (RU 486), is a steroid competitive inhibitor of the binding of glucocorticoid, androgens and progestins to their receptors. Its use in Cushing's is limited to ectopic ACTH secretion (NIEMAN et al. 1985). Doses vary from 10 to 25 mg/kg/day. A rare complication of its use is persistent hypokalemia, due to excessive activation of the mineralocorticoid receptor.

Pheochromocytoma

Pheochromocytoma is a rare catecholamine-producing tumor, encountered in sporadic or familial forms (PEDERSON and LEE 2003). Though pheochromocytoma is not a common entity, it can potentially be lethal, if left untreated (VAUGHAN 2004; VAN DER HORST-SCHRIJVERS et al. 2006). The treatment of choice for pheochromocytoma is surgical; preoperative treatment with alpha- and beta-adrenergic receptor blockers (either selective or non-selective) is nevertheless necessary even for asymptomatic patients (there is a high risk of massive catecholamines' release during surgery that can result in potentially fatal hypertensive crises and cardiac arrhythmias) (BRANDI et al. 2001).

Alpha-blockers: non-selective. Phenoxybenzamine hydrochloride is a noncompetitive alpha1- and alpha2-antagonist. Initial dose is 10 mg twice daily, with a gradual increase up to 80-100 mg daily. Maximum antihypertensive action needs 2-3 weeks to attain (PEDERSON and LEE 2003). Dose titration is done with orthostatic hypotension and reflex tachycardia as endpoints (PACAK 2007). Side-effects include sedation and postoperative prolonged hypotension. Retrospective studies have indicated that phenoxybenzamine is effective in reducing operative mortality (MANELLI 2006; PACAK 2007). Phentolamine is an alpha2-receptor blocker used in hypertensive attacks (STEINSAPIR et al. 1997). It has a shorter duration of action and dose titration can be achieved more quickly.

Alpha-blockers: selective. Prazosin, terazosin or doxazosin, all selective alpha1-blockers, have a short duration of action and do not produce reflex tachycardia (PACAK 2007). One to 6 mg of doxazosin can be given once daily (VAN DER HORST-SCHRIJVERS et al. 2006). Prazosin, has a very short half-life and needs to be administered 3 to 4 times daily.

Beta-blockers. Beta-blockers are used to control tachycardia and prevent cardiac arrhythmias, however their effect is achieved only if adequate alpha-blockade has been obtained (otherwise alpha-receptor-mediated vasoconstriction cannot be countered by vasodilation, through beta-receptor action, exacerbating hypertension) (MANELLI 2006). Propranolol, atenolol and metoprolol are commonly used. Caution is warranted while using beta-antagonists in patients with left ventricular dysfunction. Labetalol is a combined alpha- and beta-antagonist (it can be used with phentolamine in hypertensive crises (PACAK 2007)). Esmolol, a cardioselective beta1-blocker, can be given intravenously in cases of

atrial fibrillation or flutter, after sufficient alpha-blockade (BROWERS et al. 2003).

Calcium channel blockers. Calcium channel blockers cause smooth muscle relaxation in peripheral and coronary arteries through inhibition of the epinephrine-stimulated calcium influx. They should be used with caution in patients with left ventricular dysfunction. Good results with the intraoperative use of nicardipine in patients with pheochromocytoma have been reported (LEBUFFE et al. 2005).

Other medications. Metyrosine (alpha-methyl-para-tyrosine) is a competitive inhibitor of tyrosine hydroxylase, the key-enzyme involved in catecholamine synthesis that catalyses the conversion of L-tyrosine to L-Dopa. Dosage ranges from 250 mg to 1 g/day; maximum reported dose is 4 g/day and patients have tolerated the drug for up to 10 years. Its use in combination with alpha-blockers permits satisfactory preoperative management of hypertension in patients with pheochromocytoma (STEINSAPIR et al. 1997); the addition of metyrosine to phenoxybenzamine results in good intraoperative blood pressure control (LOCH et al, NICHOLSON JP Jr et al). Side-effects include fatigue, diarrhea, anxiety, depressive mood and crystalluria (VAN DER HORST-SCHRIJVERS et al. 2006). It can be used in patients with unresectable disease to keep symptoms and catecholamine secretion at bay.

Hyperaldosteronism

Primary hyperaldosteronism is characterized by excessive aldosterone production caused by a unilateral aldosterone-producing adenoma (Conn's syndrome), or rarely, carcinoma, bilateral cortical nodular hyperplasia (idiopathic hyperaldosteronism/nodular hyperplasia), or glucocorticoid-remediable aldosteronism (due to ectopic synthesis of aldosterone in the zona fasciculata; familial hyperaldosteronism type I) (MANTERO et al. 2007). Five percent to 13% of patients with hypertension have primary hyperaldosteronism; it is the most common form of secondary hypertension (CALHOUN 2006). Secondary hyperaldosteronism follows activation of the renin-angiotensin system, due either to primary overproduction of renin (by rare tumors; primary reninism) or to overproduction of renin secondary to decreased renal flow and/or decreased perfusion pressure.

For most causes of hyperaldosteronism treatment is surgical, however, bilateral idiopathic hyperaldosteronism and glucocorticoid-remediable aldosteronism are treated medically (YOUNG 2007). Furthermore, even

an aldosterone-producing adenoma may be treated medically, provided a mineralocorticoid receptor antagonist is used. Bilateral adrenal hyperplasia can be treated with spironolactone or the potassium-sparing triamterene or amiloride. In general, therapy includes low sodium diet (<100mEq of sodium per day) and administration of an aldosterone antagonist, such as spironolactone (PIMENTA and CALHOUN 2006) given at 25-100 mg three times/day, aiming to control hypertension and hypokalemia. Blood pressure needs 1-2 months of treatment to normalize, whereas hypokalemia normalizes swiftly. Such a regimen can either be used for preoperative preparation or for maintenance treatment; after several months of therapy daily dose may be titrated to 25-50 mg, aiming to a high-normal serum potassium level (YOUNG 2003b). Spironolactone therapy may have unpleasant side effects in men, in particular breast tenderness and/or gynecomastia (these are usually dose-dependent; even mastectomy may be considered) and decreased libido and impotence (caused by the inhibition of both testosterone's synthesis and of androgens' peripheral action). Women may suffer menstrual irregularity (PIMENTA and CALHOUN 2006). Hyperkalemia can be kept at bay with a thiazide diuretic. Hyperkalemia may be more prominent in older patients as well as in patients with diabetes; for these patients frequent monitoring of serum potassium and creatinine, particularly during the first month of treatment, is mandatory (for these patients, spironolactone's starting dose can be 12.5 mg daily) (PIMENTA and CALHOUN 2006). For older patients on spironolactone physicians should bear in mind that this medication prolongs the half-life of digoxin.

Eplerenone is a steroid-based selective aldosterone receptor antagonist; its affinity for the progesterone and androgen receptors is very low. It is approved for the treatment of uncomplicated essential hypertension, given at a maximum dose of 100 mg/day (JANMOHAMED and BOULOUX 2006). It has few side-effects (including dizziness, headache, fatigue, diarrhea, hypertriglyceridaemia and elevated liver enzymes) and it could be a therapeutic option for hyperaldosteronism, although results of trials comparing it to spironolactone are pending (YOUNG 2003a; YOUNG 2007). Compared to eplerenone, spironolactone has a stronger therapeutic effect, whereas potassium monitoring is not waived with eplerenone.

In patients that cannot tolerate spironolactone, the use of amiloride (at 10-30 mg/day) along with other anti-hypertensive medications is another treatment option; hypokalemia is corrected within days. Amiloride acts as an indirect mineralocorticoid antagonist; although

it well tolerated its use may lead to hyperkalemia. In some patients with idiopathic hyperaldosteronism calcium channel blockers (calcium is involved in the final common pathway of aldosterone's production) and angiotensin-converting enzyme (ACE) inhibitors (since in idiopathic hyperaldosteronism aldosterone production appears to be sensitive to the low concentrations of angiotensin II (PADFIELD 2003)) have been used effectively.

In patients with confirmed glucocorticoid-remediable aldosteronism, treatment consists of physiological doses of short-acting glucocorticoids (prednisone or hydrocortisone). Attention must be given to dosage to avoid overtreatment, particularly in children to prevent linear growth retardation (YOUNG 2003b). Secondary hyperaldosteronism is treated by way of dealing effectively with its primary cause.

Adrenocortical carcinoma

Adrenocortical carcinoma is rare, with incidence estimated at 1 case per 1.7 million (VAUGHAN 2004). Tumors can be functional (causing most often Cushing's syndrome, virilization in females, feminization in males, hyperaldosteronism or combining features of different tumors) or nonfunctional. Treatment of adrenal carcinoma is surgical removal of the primary tumor and – if feasible – of metastatic foci, since by the time of diagnosis only 30 % are limited to the adrenal (NORTON 2005). Overall five-year survival approaches 25 % (SCHULICK and BRENNAN 2003).

Mitotane (1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)-ethane or o',p'-DDD), is an isomer of the insecticide DDT. It has an adrenolytic-cytotoxic action that is relatively selective for the glucocorticoid-secreting zone of the adrenal cortex (although it can also inhibit steroid production in the zona glomerulosa). Mitotane suppresses cortisol production and decreases plasma and urine steroid levels. Mitotane is administered 3 to 4 times/day with doses reaching 6g/day (if it is well tolerated) (LUTON et al. 1990; BERTHERAT et al. 2007). Surprisingly, in some patients, mitotane was given for more than fifteen years, with good tumor response (ILIAS et al. 2001). Dosing is titrated by assessing plasma and urinary cortisol levels (MANSMANN et al. 2004). Gastrointestinal side effects include anorexia, diarrhea or vomiting, while neuromuscular untoward effects include lethargy, somnolence, dizziness or irritability. In more than 500 cases reported in the literature mitotane was shown to induce tumor response. How-

ever, despite its relatively widespread use and reported inhibition of steroidogenesis and/or primary tumor and metastatic regression, survival *per se* of treated patients with adrenal cancer has not been prolonged. Despite this shortcoming, mitotane can be given adjunctively after tumor resection (MANSMANN et al. 2004).

In a recent trial erlotinib and gemcitabine had practically no effect on advanced adrenocortical cancer (QUINKLER et al. 2008; doi:10.1210/jc.2007-2564). A trial with docetaxel and cisplatin is currently recruiting patients in Denmark (principal investigator: G. DAUGAARD, MD; gedske.daugaard@rh.regionh.dk). In another ongoing trial in the United States bevacizumab (an angiogenesis

inhibitor) is planned to be given as a single agent to patients with adrenocortical cancer (principal investigator: V. SAMNOTRA, MD; vivek.samnotra@hitchcock.org). Adrenocortical cancers express epidermal growth factor receptor (EGFR) and the use of gefitinib (IRESSA, ZD 1839), which blocks the tyrosine kinase domain of EGFR, is being investigated for such cancers (principal investigator: V. SAMNOTRA, MD). No single drug is overall effective for medical therapy of adrenocortical cancer; more studies are needed to establish novel approaches. Unresectable tumors or osseous metastases may alternatively be treated by radiation therapy (4200-5200 rads over 4 weeks).

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