Clinical Management of Adrenocortical Carcinoma (ACC)
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Disclosures

**Exelixis:**
Research support

**HRA Pharma Rare Diseases:**
Consultant

**Corcept Therapeutics:**
Consultant

**Calico:**
Consultant
Objectives

- Review the epidemiology, clinical features, diagnosis, staging, and prognosis of adrenocortical carcinoma
- Summarize the management of advanced adrenocortical carcinoma
- Discuss the use of mitotane in ACC (dosing, adverse effects, and monitoring)
Introduction to ACC
Definition
Epidemiology
Epidemiology of ACC

ACC: malignant tumor of the cortex

Adrenocortical carcinoma (ACC) is a malignant tumor of the adrenal cortex

ACC is an orphan disease
- Incidence: 1-2/million/year
- ACC affects more women than men (ratio: 1.5:1)

It has a bimodal distribution
- Adults 40-55 years old
- Children younger than 10 years

Worldwide incidence in children: 0.2 to 0.3 per million per year (although may be higher in particular populations)

ACC: adrenocortical carcinoma

Diagnosis
Work-Up
Imaging
# Diagnostic work-up for ACC

<table>
<thead>
<tr>
<th>Hormonal work up</th>
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</table>
| **Glucocorticoid excess** | • 1-mg dexamethasone suppression test or free cortisol in 24-h urine<sup>1</sup>  
• Basal ACTH (plasma)<sup>2</sup> |
| **Sex steroids and steroid precursors<sup>3</sup>** | • DHEA-S  
• 17-OH-progesterone  
• Androstenedione  
• Testosterone (only in women)  
• 17-beta-estradiol (only in men and postmenopausal women)  
• 11-deoxycortisol |
| **Mineralocorticoid excess** | • Potassium  
• Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalaemia) |
| **Exclusion of a pheochromocytoma** | Fractionated metanephrines in 24h urine or free plasma-metanephrines |
| **Imaging** | • CT or MRI of abdomen and pelvis  
• Chest CT  
• FDG-PET/CT<sup>4</sup>  
• Bone or brain imaging (when skeletal or cerebral metastases are suspected) |

1. The 1-mg dexamethasone test is the preferred method to exclude relevant hypercortisolism. However, if overt Cushing syndrome is evident, then cortisol in 24-h urine might be at least as good to quantify the cortisol excess. Alternatively, salivary or serum bedtime cortisol can be used.

2. ACTH can be skipped if hypercortisolism is excluded.

3. The most suitable set of precursors and sex hormones has not yet been established and local availability might be taken into account.

4. The panel did not agree on the systematic use of FDG-PET/CT.

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Imaging Diagnosis

Computed tomography scan showing large adrenocortical carcinoma, with internal haemorrhage, necrosis, and calcification

Computed tomography scan with axial view of left adrenocortical carcinoma

Staging classification
Prognostic factors
Staging systems for ACC

<table>
<thead>
<tr>
<th>Stage</th>
<th>ENSAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>T1–2, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T3–4, N0, M0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>T1–4, N0–1, M1</td>
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</tbody>
</table>

T1: ≤5-cm tumour; T2: >5-cm tumour; T3: tumour infiltration into surrounding tissue; T4: tumour invasion into adjacent organs; N0: no positive lymph nodes; N1: positive lymph node(s); M0: no distant metastases; M1: presence of distant metastasis

ENSAT requires extensive imaging; systematic lymph node resection; a complete surgical and pathological reports.

Prognosis

Prognosis of ACC is generally poor and depends on the stage\(^1\)

- Diagnosed at advanced stages in older series, but in the recent ones, highest percentage of patients were diagnosed in stage II through available imaging technology

Prognosis depends on stage\(^3\)

- ACC has a poor prognosis
- Overall survival at 5 years is 13%-82%

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year stage-dependent survival</th>
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<tbody>
<tr>
<td>I</td>
<td>82%</td>
</tr>
<tr>
<td>II</td>
<td>61%</td>
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<tr>
<td>III</td>
<td>50%</td>
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<tr>
<td>IV</td>
<td>13%</td>
</tr>
</tbody>
</table>

Disease-specific survival according tumour stage\(^2\)

ACC: adrenocortical carcinoma

2. Fassnacht M. Allolio B Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 273-289
### Hormonal Overproduction in ACC

<table>
<thead>
<tr>
<th>Study</th>
<th>NF</th>
<th>Cortisol</th>
<th>Androgens</th>
<th>Estrogens</th>
<th>Mineralocorticoid</th>
<th>Mixed</th>
<th>Precursors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adapted from Ayala-Ramirez et al</strong></td>
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<tr>
<td><em>EJE</em>, 2013</td>
<td>58%</td>
<td></td>
<td>23%</td>
<td>7%</td>
<td></td>
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<tr>
<td><strong>Adapted from Abiven et al.</strong></td>
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<td><em>JCEM</em>, 2006</td>
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<tr>
<td><strong>Adapted from Berruti et al.</strong></td>
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<tr>
<td><em>European Urol</em>, 2014</td>
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</tr>
</tbody>
</table>

Adapted from Ayala-Ramirez et al *EJE*, 2013
Adapted from Abiven et al. *JCEM*, 2006
Adapted from Berruti et al. *European Urol*, 2014
Prognostic Factors: Hormonal Activity

MV analysis: HR: 1.30; 95% CI, 1.04-2.62; \( p = 0.02 \)

Ayala-Ramirez et al. *EJE*, 2013


Vanbrabant et al. *EJE*. 2018

RR of cortisol production for Recurrence Free Survival

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication Year</th>
<th>Publication</th>
<th>( \text{Relative risk} (95% \text{ CI}) )</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berruti</td>
<td>2013</td>
<td>624</td>
<td>1.30 (1.04, 1.62)</td>
<td>54.34</td>
</tr>
<tr>
<td>Else</td>
<td>2014</td>
<td>391</td>
<td>1.49 (1.11, 2.00)</td>
<td>35.09</td>
</tr>
<tr>
<td>Morgenis</td>
<td>2016</td>
<td>234</td>
<td>2.05 (1.16, 3.62)</td>
<td>10.57</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td>1.43 (1.18, 1.73)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Unadjusted estimates

| Berruti      | 2013            | 624         | 1.04 (0.97, 1.12)                | 35.06   |
| Else         | 2014            | 391         | 1.04 (0.98, 1.11)                | 35.45   |
| Morgenis     | 2016            | 234         | 1.70 (1.33, 2.30)                | 19.89   |
| -            |                 |             | 2.59 (1.57, 4.27)                | 9.61    |
|             |                 |             | 1.26 (1.01, 1.51)                | 100.00  |
Prognostic Factors: Proliferation Rate (Ki67%)

Ki-67 immunohistochemistry has been proposed for prognosis purpose\(^1\)

• The Ki-67 protein is highly expressed in cycling cells\(^1\)
• It has thus been reliably used as a proliferation marker for grading multiple cancers and differentiating benign from malignant cancer\(^2\)

Prognostic Factors: **Proliferation Rate (Ki67%)**

**German cohort**

**Validation cohort**

Major Prognostic Role of Ki67 in Localized Adrenocortical Carcinoma After Complete Resection

Prognostic Factors: Resection Margin

Effect of resection Margin on local recurrence
(R0: negative margin) vs. (R1: microscopically positive)
European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors.

Recommended treatments for Localized ACC

• Preoperative Management
• Surgical Management
• Surveillance
Recommendations advanced ACC not amenable to Resection

1. Only in selected patients (with severe hormone excess)

2. The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index

3. The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index, and importantly kinetics of tumor growth

4. Radiotherapy, radiofrequency ablation, cryo-ablation, microwave ablation, (chemo-) embolization

5. Few panellists favored cisplatin + etoposide

6. Contact specialized center

ACC: adrenocortical carcinoma; EDP: etoposide, doxorubicin, cisplatin

Systemic Chemotherapy: FIRM-ACT Trial
EDP-Mitotane vs. Sz-Mitotane

- Response Rate 23% vs. 9%
- Median PFS 5 vs. 2.1 months
- Overall Survival 14.8 vs. 12 months

Fassnacht et al. *NEJM*, 2012
Only FDA approved treatment for inoperable, functional or nonfunctional, adrenal cortical carcinoma (ACC)

WARNINGS: ADRENAL CRISIS IN THE SETTING OF SHOCK OR SEVERE TRAUMA: In patients taking LYSODREN, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired. Administer hydrocortisone, monitor for escalating signs of shock and discontinue LYSODREN until recovery.
Mitotane
Mechanism of Action
Mitotane is an Adrenal Cytotoxic Agent and Steroidogenesis Inhibitor

The mode of action is not fully understood\textsuperscript{1}

Data available suggest that mitotane:

• Modifies the peripheral metabolism of steroids and inhibits key enzymatic steps in cortisol synthesis\textsuperscript{2}

• Directly suppresses the adrenal cortex\textsuperscript{2}

Administration of mitotane alters the extra-adrenal metabolism in man, leading to:

• A reduction in measurable 17-hydroxy corticosteroids\textsuperscript{3}

• Increase of 6-β-hydroxycortisol (inactive metabolite)\textsuperscript{3}

\textsuperscript{1}Lysodren® U.S. Package Insert
\textsuperscript{2}Hahner, Fassnacht. \textit{Curr Opin Investig Drugs}, 2005
\textsuperscript{3}Fassnacht, Allolio. \textit{Best Prat Res Clin Endocrinol Metab}, 2009
Improvements in the Understanding of Mitotane’s MOA

Original Research

• Mitotane alters mitochondrial respiratory chain activity by including cytochrome c oxidase defect in human adrenocortical cells¹

• Morphofunctional effects of mitotane on mitochondria in human adrenocortical cancer cells²

• Mitotane inhibits Sterol-O-Acyl Transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in ACC cells³

Mitotane Dosing and Plasma Monitoring
Mitotane PK

- Lipophilic and is stored in adipose tissues, fat is the primary site of distribution
  - Prolonged half-life: median 53 days, range (18 – 159 days)
    - This delays the impact on mitotane plasma levels after dose changes and after treatment discontinuation
  - Long onset of action (3-5 months)
    - Fat tissue can act as a reservoir for mitotane, resulting in a prolonged half-life and potential accumulation of mitotane. Despite a constant dose, mitotane levels may increase. Monitoring of mitotane plasma levels (e.g. every two months) is recommended after interruption of treatment, as prolonged release of mitotane can occur.
  - Caution and close monitoring of mitotane plasma levels are highly recommended when treating overweight patients

1. Lysodren® U.S. Package Insert
2. Paragliola et al. Eur Endocrinol, 2018
Mitotane Dosage & Administration

- Initial dose: 2 to 6 grams orally daily, in 3 or 4 divided doses\(^1\)
- Co-administer with fat-rich foods is recommended due to its lipophilic property\(^2\)

\[2-6 \text{ g/day} / 3-5 \text{ months}\]^1

Increase dose incrementally to achieve a blood concentration of **14 to 20 mg/L** or as tolerated. It can take 3 to 5 months\(^1\).

**Optimal Blood Concentration**

- Imaging assessment with thorax, abdomen and pelvis CT every 3 months for 2 years\(^2\).

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1. Lysodren® U.S. Package Insert
Mitotane Plasma Level Monitoring is to be performed on a regular and individual basis to reach/maintain an optimal therapeutic window\(^2\)

**Greater Tumor Response**
\[ \geq 14 \text{ mg/L} \]

**THERAPEUTIC WINDOW**
\[ 14 - 20 \text{ mg/L} \]

**Increased Risk of Neurotoxicity**
\[ > 20 \text{ mg/L} \]

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1. Lysodren® U.S. Package Insert
Mitotane Warnings
Precautions
Mitotane – Indication, Warnings/Precautions

Indicated for the treatment of inoperable ACC of both functional & non-functional types

**WARNINGS:** ADRENAL CRISIS IN THE SETTING OF SHOCK OR SEVERE TRAUMA: In patients taking LYSODREN, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired. Administer hydrocortisone, monitor for escalating signs of shock and discontinue LYSODREN until recovery.

- CNS Toxicity
- Adrenal Insufficiency
- Embryo-Fetal Toxicity
- Ovarian Macrocysts in Premenopausal Women

For more information please refer to the full U.S. Prescribing Information
Adrenal Insufficiency

• Mitotane is an adrenal cytolytic drug\(^1\)
• Generally spares the zona glomerulosa with selective loss of ACTH dependent adrenal zones (fasciculata and reticularis)\(^1\)
• In addition the drug inhibits key steroidogenic enzymes, most notably CYP11A1, decreasing conversion of cholesterol to pregnenolone\(^2\)
• Consider beginning hydrocortisone replacement at the outset of mitotane therapy. Mitotane is strong inducer of Cytochrome P4503A4 (CYP3A4)\(^3\)
• Causes rapid inactivation of >50% administered hydrocortisone\(^3\)
• Usually requires at least double usual maintenance dose (i.e. 40-50 mg hydrocortisone a day in divided doses)\(^3\)

1. Hahner S, Fassanacht M. Curr Opin Investig Drugs, 2005
Mitotane Drug Interactions

- **Warfarin:**
  Mitotane has been reported to accelerate the metabolism of warfarin\(^1\)

- **CYP 3A4 Substrates:**
  Mitotane is a strong inducer of cytochrome P450 3A4\(^1\)

- **Hormone Binding Protein:**
  Mitotane has been shown to increase plasma levels of sex hormone binding proteins\(^2\)

1. Lysodren® U.S. Package Insert
Adverse Events and Monitoring Plan
Mitotane Adverse Events

Most Common Adverse Effects

• Anorexia, nausea, vomiting, and diarrhea (80%)
• Depression, dizziness, or vertigo (15%-40%)
• Rash (15%)
• Neutropenia
• Hepatitis, elevation of liver enzymes
• Growth retardation, hypothyroidism
• Confusion, headache, ataxia, mental impairment, weakness, dysarthria
• Maculopathy
• Hypercholesterolemia, hypertriglyceridemia
• Decreased blood androstenedione and decreased blood testosterone in females, increased sex hormone binding globulin in females and males, decreased blood free testosterone in males
• Gynecomastia

Less Common Adverse Effects

• Hypertension
• Orthostatic hypotension, flushing
• Generalized aching, and fever
• Visual blurring
• Diplopia
• Lens opacity, retinopathy
• Prolonged bleeding time
• Hematuria
• Hemorrhagic cystitis
• Albuminuria
## Suggested Monitoring Plan

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Hematological toxicity</td>
<td>Q 3 months</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Monitor steroid replacement</td>
<td>Q 1-3 months</td>
</tr>
<tr>
<td>ACTH, Plasma Renin Activity</td>
<td>Monitor steroid replacement</td>
<td>Q 1-3 months</td>
</tr>
<tr>
<td>LFTs</td>
<td>Hepatic toxicity</td>
<td>Q 3 months</td>
</tr>
<tr>
<td>TSH, Free T4</td>
<td>Hypothyroidism</td>
<td>Q 3 months</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>Hyperlipidemia</td>
<td>Q 3 months</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Hypogonadism</td>
<td>If clinically indicated</td>
</tr>
</tbody>
</table>
| Mitotane level               | Titrate dose                | • Q month till reaching level then q 2-3 months  
                             |                              | • PRN if suspected toxicity |

Hahner, Fassnacht. *Curr Opin Investig Drugs*, 2005
Summary

• A multidisciplinary team is needed to manage the complex medical issues seen in advanced ACC
• While there are no prospective data regarding hormonal management in ACC, therapy is suggested based on ESE/ENSAT 2018 guidelines
• Mitotane use should be supervised closely to achieve desired plasma level 14-20 mg/L and monitor adverse events
• Adrenal insufficiency is among the most common side effects during mitotane therapy and often requires higher than the average steroid replacement

Clinical Management of ACC

THANK YOU!