Adrenocortical Carcinoma

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KEYWORDS

• Adrenocortical carcinoma • Prognosis • Predictors • Surrogate • Survival • Metastasis • Mitotane • Chemotherapy

KEY POINTS

- Major breakthroughs have been achieved in the identification of relevant molecular alterations in adrenocortical carcinoma, but no simple actionable target has emerged.
- Progresses in the prognostic risk stratification constitute the basis of future stratified medical strategies and evaluations.
- Making therapeutic advances against adrenocortical carcinoma is a formidable challenge facing patients and clinicians with expert centers and networking as a basis of progress.
- R0 surgery of more than 90% of localized ACC patients is a unmet need.

Adrenocortical carcinoma (ACC) originates from the adrenal cortex and is typically defined by positive immunostaining for steroidogenic factor 1 (SF1), melanA (Mart1) markers but without staining for cytokeratins and chromogranin A.[1–4] As for all endocrine tumors, malignancy is ascertained by the presence of local or distant spread. No absolute criteria of malignancy exists for the diagnosis of ACC in those tumors confined to the adrenal gland, but a Weiss score of 3 or higher is generally considered to establish the diagnosis.[3,4] In addition, several studies have shown that a Ki67 index higher than or equal to 2.5% to 5% was associated with an abnormal Weiss score or a higher risk of recurrence.[5–9]

The incidence of ACC is less than 0.7 to 1.5 per 1 million people per year.[10–12] Because of the low incidence of ACC, a limited number of prospective studies have investigated potential therapies. In addition, the use of mitotane, a major drug

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metabolism inducer but also a drug with delayed antitumor activity, in most patients with ACC makes the conclusions from previous trials uncertain. Thus, advances in the understanding and management of ACC largely depend on the history of mitotane prescription, findings in retrospective studies, expert consensus, and clinicians' experience from expert centers. The implementation of networks for ACC, such as the European Network for the Study of Adrenal Tumors (ENSAT), the demonstration of the feasibility of phase 3 trials but also recent recommendations, constitute major steps forward.[3,4] This review focuses on the therapeutic management of adult patients with sporadic ACC.

CHARACTERIZATION BEFORE THERAPY

ACC must be precisely characterized according to standardized criteria as defined by ENSAT and the European Society for Medical Oncology recommendations.[4] Although the criteria are simple, lack of accurate characterization of patients with ACC in most retrospective studies, including absence of Weiss criteria, proliferative index, and resection status (R status), makes their final conclusions uncertain.

The minimum information that should be included in records of all patients with ACC is given in **Box 1**. Genetic disorders that affect less than 5% of adult patients with ACC are looked for in case of familial history or age younger than 40 years at diagnosis and have been extensively reviewed recently.[13] Approximately 80% of patients with ACC present with symptoms (tumor burden or hormone-related manifestations)[14–19] and two-thirds of patients with ACC produce steroids.[20] ACC hypersecretion can concern both active steroids (mainly glucocorticosteroids and

Box 1
Parameters to be characterized in patients with ACC at the time of therapeutic interventions

- Age and comorbidity, genetic background, performance status
- Weiss global score, including the precise count of mitosis/50 HPF
- Percentage of Ki 67 index in the most active regions (number of cells analyzed to be specified)
- Presence of tumor-related or hormone-related symptoms
- Secretory status: type and magnitude of secretions
- c/pTNM UICC and/or ENSAT staging including:
  - Modality of imaging
  - Disease-free interval
  - Number and location of abnormal lymph nodes at imaging or positive at pathology
  - Presence and type of venous invasion or adjacent organ invasion
  - Number and type of tumor organs
- Resection status of the primary, number of lymph nodes resected, tumor spillage/hemorrhage during surgery
- Mitotane history, highest plasma level reached in case of second-line therapy
- Signed informed consent for bioresource use when available

Abbreviations: c/p, clinical/pathological; HPF, high power field.