Decision-making for adrenocortical carcinoma: surgical, systemic, and endocrine management options.

DECISION-MAKING FOR ADRENOCORTICAL CARCINOMA: SURGICAL, SYSTEMIC, AND ENDOCRINE MANAGEMENT OPTIONS

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Summary

Introduction. Adrenocortical carcinoma (ACC) is a rare tumor characterized by poor prognosis in most cases. Moreover, in most cases ACC produces an excess of adrenal steroid hormones with relevant clinical consequences.

Areas covered. After an extensive literature search, this narrative review addresses diagnostic management, including hormonal, radiological and pathological assessment, and treatment, which should be directed toward both cancer and hormone related problems. While surgery is the first option in ACC without evidence of metastatic disease, and the only possibility of cure, the therapeutic management of metastatic patients is centered on systemic therapy including mitotane alone or in combination with chemotherapy. Mitotane is also used in adjuvant setting, because up to 80% of patients with non-metastatic ACC show loco-regional or distant metastases after an apparent complete surgical excision.

Expert Commentary: Management of ACC patients is fraught with many difficulties and should be limited to experienced physicians. Each step of clinical management, such as diagnosis, prognostication, treatment (both surgical and medical) is challenging and carries the possibility of severe mistakes. For this reasons, each step of the management strategy should be decided in the setting of a multi-disciplinary team including different expertise (endocrinology, radiology, pathology, oncology), in expert centers.

1. DIAGNOSIS

Adrenocortical carcinoma (ACC) is a rare tumor (0.5-2 cases per million per year) **with a peak incidence between 40-60 years, and with women being more affected (55-60%) [1, 2]. ACC is characterized by a poor prognosis in most cases [3]. However, prognosis is heterogeneous** being mainly influenced by tumor stage at diagnosis (5-year survival rate is 81, 61, 50, and 13 %, respectively, from stage 1 to stage 4) and completeness of surgical

extirpation [4]. **ACC usually present as a sporadic tumor, but can be encountered in the setting of hereditary tumor syndromes, such as Li Fraumeni (TP53 germline and somatic mutations), familial adenomatous polyposis coli (β-catenin somatic mutations) and Beckwith–Wiedeman (IGF-2 overexpression) [5]**

The diagnostic approach to any adrenal mass should include use of high-resolution imaging techniques to ascertain the risk of malignancy. In current practice, CT is the most frequently used test for this aim and also for staging purpose. MRI and FDG-PET are often used as second-line tests, when CT findings are inconclusive [3, 6-8]. There is still insufficient evidence to judge which modality is superior [9]; however, unenhanced CT is generally considered the primary imaging test to exclude an adrenal malignancy, in presence of a homogeneous adrenal mass with density ≤ 10 Hounsfield Units and size ≤ 4 cm [7]. When an adrenal mass is suspected to be an ACC, it is key to conduct a full staging by extending imaging evaluation to the thorax and pelvis, since ACC may present with distant metastases in about 25% of cases [3, 4, 6, 7, 8].

ACC has the propensity to produce and secrete steroids; thus, in all patients with suspected ACC, signs and symptoms of cortisol, aldosterone, and sex steroids should be actively investigated [6]. Concomitant secretion of different steroids is a hallmark of ACC. The most frequent condition is a cortisol-secreting ACC causing a Cushingoid phenotype including facial plethora, easy bruising, weight gain, proximal myopathy, severe hypertension and uncontrolled diabetes mellitus. Hypokalemia is common with severe hypercortisolism because mineralocorticoid receptors are triggered by the large amount of cortisol that overwhelms the inactivating capacity of corticosteroid 11β-dehydrogenase isoenzyme 2 (HSD11B2). Women frequently complain of acne, hirsutism, and oligomenorrhea [3]. The differential diagnosis in these situations is PCOS, especially with mild or subclinical hypercortisolism. Clinical clues that are helpful to the diagnosis of ACC are the concomitant

existence of a Cushingoid phenotype with signs of marked androgen excess, with cancer-related symptoms (anorexia, cachexia, mass effect). With rapidly growing tumors, cancer-related features dominate the clinical presentation. ACC can also cause deep venous thrombosis or pulmonary embolism due to either cortisol excess or malignancy [3]. Moreover, the presence of cortisol excess may consistently increase the toxicity of chemotherapy since it is associated with immune depression that may favor infections particularly in the neutropenia phase. Cortisol excess should be excluded in all patients with suspected ACC, even if they do not present with typical Cushing features [7].

A detailed hormonal work-up (**Table 1**) should be performed preoperatively in all patients with suspected ACC for the following reasons:

i) Demonstration of steroid excess establishes the adrenocortical origin of the tumor, while other differential diagnoses are being ruled out (i.e. lymphoma, sarcoma);

ii) The steroid profile may be helpful to evaluate the malignant potential (i.e. estradiol excess in males, high concentration of dehydroepiandrosterone sulphate –DHEAS- or steroid precursors);

iii) Presence of autonomous cortisol secretion in a patient with ACC indicates a risk of post-operative adrenal insufficiency, which can be potentially life-threatening;

iv) Demonstration of steroid excess at baseline establishes tumor markers that can be useful to detect persistence or recurrence of disease postoperatively [3, 8].

A standard 1 mg overnight dexamethasone test (1-mg DST) is recommended to exclude **autonomous cortisol secretion in accordance with low or suppress levels of ACTH**, similar with adrenal incidentaloma [7] This test has higher sensitivity (95% at a cortisol threshold of 1.8 μg/dL), compared with 24-h urinary-free cortisol (UFC) which is not helpful

in cases of mild hypercortisolism [10]. If cortisol levels following the 1-mg DST are not suppressed despite lack of **overt Cushing syndrome**, the condition of autonomous cortisol secretion may be present. The recent guidelines of the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENSAT) promoted this definition to the classic "subclinical Cushing's syndrome" [7]. Autonomous cortisol secretion is certain for a cortisol levels above 5 μg/dL after 1-mg DST, while values between 1.8 μg/dL and 5 μg/dL require additional investigation to confirm the diagnosis **[7]**. Recognizing asymptomatic cortisol excess preoperatively identifies the patients who benefit from glucocorticoid replacement **in anesthesia induction and after adrenalectomy and during follow-up** [11]. Aldosterone-producing ACC is rare and is generally associated with severe hypertension and marked hypokalemia [12]. Screening by measuring plasma aldosterone and plasma renin activity (PRA) (or direct renin concentration) is recommended in all hypertensive and/or hypokalemic patients with adrenal masses [13]. In some cases, pseudo-aldosteronism is present, due to increased production of deoxycorticosterone. Pure estrogen excess is rare and may cause gynecomastia, loss of libido and testicular atrophy in men, **while in women menstrual irregularities** [8]. Hypersecretion of sexual steroids is frequently associated to cortisol excess in ACC patients. Baseline 17-OH progesterone levels are frequently increased, as well as androstenedione and DHEAS, **which leads to increased plasma testosterone in females with signs of androgen excess (hirsutism, acne, alopecia)** [3]. Measurement of steroid precursors in blood or urine may be exploited for diagnostic purposes. However, the value of increased DHEAS levels to predict malignancy of an adrenal mass is rather low [14]. More recently, it was demonstrated that serum steroid paneling by LC-MS/MS is a useful tool to discriminate ACC from other adrenal tumor lesions. In this study, both the number of steroids secreted in high amounts and the marked elevation of several steroid intermediates without biological activity was characteristic of ACC and useful for the differential diagnosis.

The cortisol precursor 11-deoxycortisol was found the most discriminating between ACC and non-ACC adrenal lesions [15].

Assessment of plasma or urine fractionated metanephrines is recommend in patients with suspected ACC to exclude a pheochromocytoma, and avoid misdiagnosis and unexpected intraoperative complications [3, 7, 16]. Pertinently, **the radiological imaging of** pheochromocytoma may appear as a large, heterogeneous and hypervascularized mass mimicking ACC **and rarely pheocromocytoma may present with hypercortisolism, being due to ectopic ACTH production [17]**.

Finally, the hormonal assessment is **fundamental** because treatment should be directed toward both cancer and hormones, and the therapeutic approach varies according to the stage at diagnosis and clinical conditions of patients. **However, it is important to recognize non-specific symptoms due to the mass effect, including abdominal discomfort (nausea, vomiting, abdominal fullness) and back pain, while classical malignancy-associated symptoms such as weight loss, night sweats, fatigue or fever are less frequently observed [8].**

All patients with suspected or proven ACC should be discussed in a multidisciplinary expert team meeting (including the following specialists: endocrinologist, oncologist, surgeon, radiologist, pathologist) at least at the time of initial diagnosis and at critical points during the disease course (e.g. tumor recurrence, progression). The team should have access to adrenal-specific expertise in interventional radiology, radiation therapy, nuclear medicine, and genetics as well as to palliative care facilities.

2. PROGNOSTIC FACTORS

ACC stage and a margin-free resection are important and validated prognostic factors [3, 4, 6]. Currently, the ENSAT staging system is the most frequently used and allows a

clear stratification of prognosis by stage [4]. Resection status Rx (unknown), R1 (microscopically positive margins) and R2 (macroscopically positive margins) are associated with progressively reduced survival irrespectively of other risk factors [3, 4, 6]. The proliferation activity of the tumor influences the risk of recurrence following R0 surgery and proliferation is currently assessed by the immunohistochemical evaluation of the Ki-67 index, despite some problems to harmonize readings among different pathologists. Higher values of Ki-67 index are consistently associated with a worse prognosis and, in a multicenter study, a Ki-67 value at 10% was found to separate patients at good or worse prognosis, in terms of risk of recurrence following complete resection [18]. Assessment of the mitotic index carries the same information, and a cutoff at >20 mitoses per 50 high-power field has been established to define high-grade tumors [19]. However, studies correlating the two proliferation indexes are lacking.

The role of overt cortisol excess as a negative prognostic factor has been consistently confirmed in a number of studies showing an association between cortisol overproduction and shorter survival. Interestingly, cortisol excess was an independent prognostic factor either in patients with advanced ACC [20, 21] or following complete tumor resection [22]. Therefore, cortisol excess confers a negative prognostic effect beyond its expected detrimental impact on patient's conditions and it is likely a hallmark of increased biological aggressivity.

3. SURGICAL TREATMENT

Surgery is the first option in ACC without evidence of metastatic disease (stages I–III) and the only possibility of cure. The 5-year survival rate is approximately 55% when radical resection is possible [23]. In patients with infiltrating tumor or suspected lymph nodes open

adrenalectomy (OA) is recommended; on the contrary, a localized ACC (I-II stage) can be removed by laparoscopic adrenalectomy (LA) or by OA [6], although the use of laparoscopic approach in this setting is still debated. Literature is indeed discordant: Huynh and colleagues [24] showed that use of LA may decrease survival **in patients with stage II** ACC, while **most of the other** studies failed to demonstrated significant different outcomes between LA and OA [25-28]. **In these studies, the recurrence rate was 54%, 50%, 53%, and 49%, respectively, after LA compared to 61%, 64%, 65%, and 64%, respectively, after OA. However, a study raised concern about the most frequent occurrence of peritoneal carcinomatosis with the use of LA [29].** However, all these studies are retrospective and likely prone to selection bias, and no prospective trials are available at this moment. Whatever the surgical approach, surgery must be performed by an extremely skilled surgical team, in centers with high volume of adrenalectomies per year [30], with the goal of a R0 resection (microscopically free margins).

Despite state-of-the-art surgery recurrence after intervention is frequent. Since an early detection of local recurrence or limited metastatic disease can open the possibility of a complete resection associated with a long RFS [31], a tight follow-up is mandatory. Hormonal assessment and imaging (total-body CT) should be done every 3 months for at least 2 years after surgery. After this period, intervals could be gradually increased, but also in patients without evidence of disease follow-up is recommended in the long period [6].

4. SYSTEMIC TREATMENT

4.1 ADJUVANT TREATMENT

Despite an apparent complete surgical excision, up to 80% of patients show loco-regional recurrence or distant metastases. To reduce the high rate of recurrence, most centers

recommend adjuvant treatment with mitotane (o,p'-DDD), available in 500-mg tablets for oral administration. Mitotane is an adrenolytic drug, a parent compound of the insecticide dichlorodiphenyltrichloroethane - DDT, able to inhibit gene expression of various cytochrome P450-dependent mitochondrial enzymes of the steroidogenetic pathway [20,22 desmolase (CYP11A1), 11β-hydroxylase (CYP11B1) and 18β-hydrolase (CYP11B2)] [32].

Use of adjuvant mitotane in ACC was first proposed by Schteingart and colleagues in 1982 [33]. No data from randomized trials are available; however, convincing results in support of adjuvant therapy with mitotane were provided by a large retrospective study of ours, including 177 patients from different Italian and German centers. A group of patients underwent adjuvant therapy with mitotane after surgery while patients of two contemporary independent control groups were followed without any therapy. Recurrence-free survival (RFS) was significantly longer ($p < 0.0001$) in the 47 patients treated with adjuvant therapy (42 months) compared to the groups of 55 and 75 patients not treated after surgery (10 and 25 months, respectively). Also overall survival (OS) was significantly prolonged in the mitotane group (110 months) compared to the two control groups (52 and 67 months, respectively) [34]. Recently, our group has updated the follow-up of these cohorts of patients with almost 10 years of additional observation, confirming that adjuvant mitotane treatment is associated with a significant benefit in terms of RFS regardless of the hormone secretory status [35]. Advantage in OS was less evident but this may be explained by the fact that mitotane was introduced as treatment of ACC recurrence in most patients. Despite its retrospective nature, this study remains the most informative piece of evidence on the topic and represents a reference for decision making in ACC patients. Strengths of the study are the inclusion of contemporary groups of matched patients, who were allocated to treatment or follow-up based on the treatment policy the center.

Conversely, in many studies patients with unfavorable characteristics were more likely selected for adjuvant mitotane, thus introducing a bias. An example of this may be found in a recent study reporting a multicenter, retrospective analysis on 207 ACC patients, showing that adjuvant mitotane was associated with decreased RFS. However, 42% of the patients treated with mitotane had stage IV ACC and, indeed, chemotherapy was frequently associated to mitotane therapy [36]. A retrospective study from the University of Michigan confirmed the finding that adjuvant mitotane treatment is associated with a significantly improved RFS although it failed to prolong significantly OS [37]. The lack of effect on OS may be explained with the short follow-up (25.6 months).

Despite controversy on this issue, there is general agreement on the adjuvant use of mitotane following surgical removal of ACC in high-risk patients. The condition of high risk of recurrence has been defined as stage III, or Ki-67 >10%, or Rx-R1 resection by a panel of international experts [38]. For low risk patients, who are characterized by stage I or II, R0 resection and Ki-67 ≤10%, adjuvant mitotane therapy is not mandatory. An international, multicentric, prospective, randomized trial (ADIUVO trial) is currently enrolling low-risk ACC patients, who are randomized to mitotane or observation, in order to definitely establish the effectiveness of adjuvant mitotane in this set of patients.

It is common practice in expert centers to monitor regularly blood mitotane concentrations during treatment and to target levels of 14–20 mg/L [39]. A retrospective analysis demonstrated that blood mitotane concentrations ≥14 mg/L were associated with a prolonged RFS in patients treated with adjuvant mitotane following macroscopically radical surgery [40]. Thus, maintenance of target mitotane concentration may represent a predictor of response to adjuvant treatment.

There is no consensus on how to start treatment: the ESMO guidelines [38] recommend that mitotane therapy should be administered following a high-dose regimen with the aim of

reaching a daily dose of 6 g/daily rather soon and then adjust the dose according to tolerability and mitotane levels. In our personal practice, we start treatment at lower doses (**Table 2**) because they are better tolerated and less patients have to discontinue treatment [29]. **Adjuvant mitotane treatment is started as soon as possible and usually no longer than 12 weeks following surgery, even if there are no data showing what is the best timing.** Duration of adjuvant mitotane therapy has not been definitively established, but it is reasonable to continue therapy for at least 2 years, because this is the period when most of ACC recurrences are detected. In our practice, we have currently extended treatment till to 3 to 5 years, if tolerated.

The most common unwanted effects are gastrointestinal manifestations that appear early in the course of treatment, independently on mitotane levels [41]. Diarrhea and nausea are particularly frequent and can be managed with temporary dose reduction and supportive therapy. Elevated g-glutamyl-transferase levels are also frequently observed but are not actually troublesome unless values are exceedingly elevated. Clinically significant liver toxicity is characterized by a marked increase in transaminases and bilirubin, but is infrequently observed in the absence of predisposing conditions [39]. Central neurologic toxicity (cerebellar symptoms, disturbed cognitive performance) is more closely associated with elevated mitotane concentrations (20 mg/L) but subtler symptoms, such as memory impairment or attention deficit, may be observed in some patients even at lower drug concentrations [42]. In this context, monitoring of circulating mitotane levels may be useful to tailor individually the therapy and limit side effects thus attaining better compliance to treatment. The implementation of blood mitotane monitoring, through a service provided in Europe by the company distributing Lysodren® (Lysosafe, www.lysodren-europe.com), has rendered the use of this drug more feasible because it is possible to some extent to anticipate and prevent toxicity. In our current practice, measurement of circulating mitotane

concentration has become mandatory for a proper management of patients with ACC. **At our center, monitoring of mitotane concentrations is done every month in the starting phase of treatment, and then every 3 months once mitotane levels are at plateau; moreover, additional monitoring is adjusted according to clinical needs. Biochemical monitoring includes also blood count, liver function tests, creatinine, electrolytes, glucose, lipids, ACTH, cortisol, PRA, testosterone, DHEAS, 17-hydroxyprogesterone, androstenedione, LH, FSH, TSH, FT4.**

A general measure to deal with mitotane toxicity is a step down to the previously tolerated dose, or temporary drug withdrawal in the event of severe manifestations (**Table 2**). However, well-informed and motivated patients are able to cope with side effects and maintain compliance to treatment. To accomplish this task, it is important to establish a close patient–physician relationship to induce and maintain adherence to treatment. Patients seek advice frequently, also because their local physicians are unfamiliar with mitotane use and its attendant complications, and it is necessary to give a timely counseling to keep patients on treatment.

Mitotane has a wide range of effects on the endocrine system and may potentially cause several endocrine disturbances that should be carefully managed (**Table 3**). Because of the adrenolytic effect of mitotane, all patients should receive glucocorticoid replacement to prevent adrenal insufficiency. Steroid doses are typically higher than in Addison's disease, due to an enhanced metabolic clearance rate of glucocorticoids induced by mitotane [3, 6, 43]. An inadequate treatment of adrenal insufficiency increases mitotane-related toxicity, particularly gastrointestinal side effects, and reduces tolerance [30]. Mineralocorticoid supplementation is not mandatory in all patients because the zona glomerulosa is partly spared by the toxic effect of mitotane [44]. Moreover, mitotane affects thyroid and gonadal function by mechanisms that are still to be completely elucidated. Mitotane administration is associated with low FT4

levels without a compensatory rise in TSH, an effect that becomes apparent early in the course of treatment. This prompts thyroxin replacement, even if the benefit of this measure may be difficult to appreciate [42, 44]. In women, gonadal function is usually preserved and most female patients have regular cycles unless PRL levels are significantly increased [6, 42, 44] due to a weak estrogen-like action of mitotane [45]. Conversely, in men mitotane treatment causes sexual dysfunction as a late but common unwanted effect, due to inhibition of testosterone secretion. Sex steroid replacement may become necessary to treat hypogonadism in some patients but may worsen gynecomastia [6, 42, 44]. Mitotane use is associated with increasing levels of LDL and HDL cholesterol, and triglycerides [46]. However, the value of introducing statins remains uncertain although patients may be worried about their lipid levels. The decision to use anti-lipid drugs, which may further complicate supportive therapy and is not exempt from potential toxicity, should be carefully though at considering patient life expectancy. **Side effects of mitotane treatment are showed in Table 4.**

Another option is adjuvant radiotherapy, that in a retrospective analysis from the United States was reported to decrease of 4.7 times the risk of local failure compared with surgery alone [47]. In a retrospective analysis from the German ACC Registry, radiotherapy in an adjuvant setting resulted in a significant better 5-year RFS, but did not affect OS and disease-free survival [48]. However, no difference between surgery plus radiotherapy and surgery alone was found in another retrospective study done in the United States [49]. A review of the literature concluded that adjuvant radiotherapy should be considered in patients with incomplete, or R1 resection, or Rx resection, who are at high risk for local recurrence [50]. A total dose of >40 Gy with single fractions of 1.8 Gy to 2 Gy should be administered. However, prospective investigations are required and no definitive conclusions are available at the moment.

As far as chemotherapy is concerned, limited data are available. A recent paper published data on 3982 ACC patients from the National US Cancer Data Base (NCDB), revealing that adjuvant chemotherapy was performed in 10% of cases. However, the study was not able to capture in how many cases cytotoxic agents or mitotane have been used as adjuvant chemotherapy. By comparing these subjects with those treated with surgery only, OS was not different, while no RFS analysis was reported [51]. Anecdotal cases reported a more favorable outcome after an adjuvant etoposide – cisplatin based chemotherapy [52]. A phase II clinical trial reported that the combination of mitotane plus streptozotocin was effective in an adjuvant setting. However, the study design does not allow discriminating the relative merits of the two drugs [53].

4.2 TREATMENT OF ADVANCED DISEASE

About 50% of newly diagnosed ACC patients present with metastatic or unresectable disease [38] and, as previously said, most ACC that underwent initial complete resection are doomed to develop recurrent or metastatic disease [38, 39]. The prognosis of patients with advanced/metastatic ACC is generally poor but it is heterogeneous and long-term survivors have been described [39, 54]. The management of these patients is mainly centered on systemic therapy including mitotane alone or mitotane in combination with chemotherapy.

The standard chemotherapy regimen for advanced ACC is EDP (etoposide, doxorubicin and cisplatin) plus mitotane (EDP-M). This scheme was introduced in a multicenter prospective phase II study conducted in Italy [20 55]. More recently, its efficacy was compared against the combination of streptozotocyn and mitotane (Sz-M) in a prospective randomized phase III clinical trial conducted worldwide [56]. Three hundred and four patients were prospectively enrolled in about 6 years. Patients with disease progression to the first-line treatment received the alternate regimen. EDP-M was superior to Sz-M both in terms of disease

response rate and progression-free survival (PFS). Analysis of OS also favored patients initially randomized to receive EDP-M but due to the attenuating effect of the cross over to EDP-M of patients who progressed to Sz-M, the difference failed to attain statistical significance. In addition to systemic therapy also loco-regional therapies, i.e. surgery [57, 58], radiofrequency ablation (RFA) [58, 59], and chemoembolization [60] can be taken into consideration in a selected patient population. Moreover, in patients, who have contraindications to EDP, or poor performance status, either cisplatin or carboplatin administered as single agents could be reasonable options.

It is worth of note that there is a small subgroup of patients with advanced/metastatic ACC presenting an oligo-metastatic disease with favorable prognostic factor and/or a relatively long disease-free interval from previous surgery (i.e. 12 months or more). These patients have a relative long survival perspective and may not benefit from an aggressive systemic treatment such as the EDP-M regimen. Therefore, single agent mitotane could be a reasonable option. Mitotane is often associated with loco-regional approaches in the treatment of these patients. Surgery of primary and or metastases can be recommended if a complete resection (R0) is achievable. Surgery of multiple metastases is considered on a case-by-case basis and should be performed mainly in patients with favorable prognostic factors, sustained disease response to systemic therapy, and long-term R0 resection expectations. In patients who are not candidates for surgery, percutaneous image-guided RFA is a locally effective treatment and chemoembolization is another possibility to treat liver metastases. RFA in combination with surgical resection may allow better disease control in the setting of limited disease [58-60]. Tumor debulking generally offers little benefit, however surgery of primary disease in newly diagnosed patients with oligo-metastatic disease and limited exta-adrenal tumor volume can be performed in case of good response to systemic therapy. It should be noted that the efficacy of local regional therapies in the management of such patients has never been

assessed in a randomized prospective clinical trial, so we cannot exclude that the long-term benefit obtained in some cases can be ascribed to a patient selection. In the author opinion, the long-term benefit is due at least in part to the efficacy of systemic therapy; therefore, it is recommended that all local regional approaches should be used in combination with systemic therapy.

On the contrary, the majority of metastatic ACC patients have poor prognostic features (i.e. 2 or more organ involved). For these patients, chemotherapy with EDP-M regimen represents the treatment of choice. In case of painful metastasis, palliative radiotherapy is an option, especially in bone lesions. Due to the latency of mitotane to attain the therapeutic range, the drug administered alone is not indicated in the management of patients with clinical evidence of fast growing tumors. Metastatic ACC submitted to EDP-M regimen have a survival perspective of 18 months as demonstrated by the results of the FIRM-ACT trial [56]. However, 15% of patients are alive after 5 years. In terms of PFS, 50% of patients submitted to EDP-M showed disease progression after 5 months, and 25% of patients were free from progression after 12 months, and 15% after 2 years. In addition, few patients were still alive and free from progression after 5 years [56]. These data show that the efficacy of chemotherapy plus mitotane is overall modest, but a small subset of patients is destined to obtain a long-term disease control. The identification of factors that may predict chemotherapy efficacy is very important to select patients destined to benefit from this aggressive strategy and to address non-responding patients to experimental therapies. In a recently published paper, our group has demonstrated that the expression of topoisomerase II was associated with EDP-M efficacy [61]. These data need confirmation. It should be noted, however, that EDP is usually administered for a maximum of 6-8 cycles while mitotane is usually maintained till progression. It is possible that cytotoxic chemotherapy is useful to attain rapid tumor shrinkage but the long-term efficacy observed in some cases could be attributed to the

mitotane maintenance. If this is true, predictive factors of mitotane efficacy are needed. Human cytochrome P450 2B6 (CYP2B6) [62] and CYP2W1 [63] that are involved in mitotane metabolism and may activate mitotane in the adrenocortical tissue, respectively, or ribonucleotide reductase large subunit 1 (RRM1) gene expression [64] are promising predictive factors of mitotane efficacy. The value of these potential predictive factors should be assessed in prospective studies.

Finally, regarding second-line therapy, the results of patients with disease progression to platinum-containing regimens plus mitotane were as a whole modest. The association of gemcitabine to metronomic capecitabine showed a limited activity in a prospective multicenter phase II trial conducted in Italy [65]. Results have been confirmed a series of patients treated in a real world practice both in Germany and in Italy [66]. This regimen still remains the most used option as second line therapy. Several small phase II trials have tested the efficacy of molecular agents targeting EGFR, angiogenesis, IGFR, and mTOR pathways. These treatments administered in pre-treated patients either alone or in combination with chemotherapy, or with other molecular target agents obtained poor results [67-69]. In a multicenter randomized phase III trial involving most referenced centers in Europe and United States, the drug Linsitinib (OSI-906), an orally available IGFR inhibitor failed to demonstrate a superiority over placebo in terms of both progression free and overall survival in advanced pre treated ACC patients [70]. Also modern immunotherapy failed to show efficacy in advanced ACC. In a phase 1b cohort (NCT01772004), 50 patients with metastatic ACC and prior platinum-based therapy received avelumab at 10 mg/kg IV every 2 weeks, until progression. Only 2 patients (5%) attained a disease response while PFS was 5.5 and 1.5 months in patients with PDL-1 positive and negative ACC patients, respectively [71].

5. ENDOCRINE MANAGEMENT OF CORTISOL SECRETING ACC

The morbidity caused by ACC and its prognosis derives not only from the spread of malignant cells into other organs but also from the consequences of hormone excess. Consequently, the goals of treatment in ACC include both control of tumor growth and mitigation of the effects derived from hormone excess in patients with hormone-secreting ACC. As uncontrolled hypercortisolism strongly impacts on quality of life and may cause a precocious death, a rapid control of hormone hypersecretion is mandatory. Mitotane has both anti-secretive and anti-proliferative activity; however, the slow onset of mitotane activity is a main limitation for the management of Cushing's syndrome [26]. Faster drug in lowering serum cortisol levels are needed, such as metyrapone, ketoconazole, etomidate [72]. A case series of 14 patients with severe neoplastic hypercortisolism, including 8 ACC, have been treated with a combination of metyrapone and ketoconazole in two tertiary-care university hospitals. In patients with ACC, median UFC after 1 week of treatment fell from 16.0 to 1.0 ULN (upper limit of the normal range) and after 1 month UFC values were normal in 86% of patients. Also important improvements of clinical status, kalaemia, glycaemia and blood pressure were reported, with decrease in drugs used for co-morbidities. Side effects were minimal and only one patient with ACC had plasma transaminase increase, necessitating ketoconazole withdrawal. The study concluded that metyrapone–ketoconazole combination is well tolerated and allows a rapid control of life-threatening ACC induced hypercortisolism [73]. Recently, Claps and colleagues [74] reported three cases of advanced ACC patients with Cushing's syndrome treated with a combination of metyrapone and EDP-M. The case series showed that this treatment was effective and well tolerated, inducing a rapid control of hypercortisolism caused by cortisol-secreting ACC.

On a separate note, it is important to offer advice about the potential concerns of becoming pregnant after removal of an ACC. There is limited evidence suggesting that

pregnancy may trigger ACC recurrence and that pregnancy in patients with past or current ACC may be associated with worse prognosis [75, 76]. Moreover, pregnancy should be avoided while being exposed to mitotane, due to its potential teratogenic effects. In this context, it is important to recognize that mitotane levels may remain measurable for many months following discontinuation of treatment.

Expert commentary:

Management of ACC patients is fraught with many difficulties and should be limited to experienced physicians. Each step of clinical management, such as diagnosis, prognostication, treatment (both surgical and medical) is challenging and carries the possibility of severe mistakes. For this reasons, each step of the management strategy should be decided in the setting of a multi-disciplinary team including different expertise (endocrinology, radiology, pathology, oncology). First, pre-surgical diagnosis should be accomplished with a number of different tests (both radiological and hormonal) in the least time possible. Second, it is of the utmost importance that surgery be done in high-volume centers to offer the best possibility of radical resection to the patients. This remains the single most important therapeutic act for ACC patients. Third, careful selection of patients for adjuvant or palliative therapies should be undertaken, and treatments should be given in expert centers. In these centers, patients may be offered the chance to participate in clinical trials with experimental drugs due to the limited availability of current therapeutic choices.

Five-year view:

Recent studies [77], [78] provided great advances in the understanding of molecular pathogenesis of ACC and led to the definition of groups characterized by different molecular signature and different prognosis. It is expected that over the next few years the use of these

molecular markers will be applicable in clinical practice thus representing the cornerstone for prognostication and stratifying treatment strategy. This will be the first step toward a personalized therapy; as instance, patients in the "good prognosis group" may be potentially spared adjuvant mitotane treatment while patients in the "poor prognosis group" may be treated more intensively. As to adjuvant mitotane treatment, the conclusion of the ongoing ADIUVO and ADIUVO-2 study, which is about to be launched, will provide important data for defining the value of adjuvant mitotane in either "low-risk" or "high-risk" patients. Finally, molecular studies will hopefully detect targets that can be druggable, thus paving the way for future targeted therapies with more efficacy and less toxicity compared to the current therapeutic options. This remains the most urgent need in the management of advanced ACC.

KEY ISSUES

- Adrenocortical carcinoma (ACC) is a rare tumor that should be diagnosed and treated promptly due to its very aggressive behavior.
- ACC is frequently associated with Cushing's syndrome that may have severe clinical consequences, including a strong impact on quality of life and reduction of life expectancy.
- Surgery is the treatment of choice and should be attempted whenever radical resection is feasible.
- Despite radical surgery, ACC has a high propensity to recur, particularly when adverse prognostic factors are present.
- Mitotane is the only approved drug for ACC and is used either as adjuvant treatment following surgical removal of the tumor or palliative treatment for advanced disease.
- Mitotane is a difficult drug to manage and either monitoring of circulating levels or institution of appropriate supportive therapy is a key to limit drug-related toxicity.

- Standard treatment of advanced ACC includes the chemotherapy regimen EDP (etoposide, doxorubicin, cisplatin) in association with mitotane.
- Medical treatment of ACC is still underdeveloped and has limited efficacy. Hypercortisolism should be promptly corrected by using mitotane in combination with a faster inhibitor of steroidogenesis, such as metyrapone.

Reference annotations: please highlight 6–8 references that are of particular significance to the subject under review as "* of interest" or "** of considerable interest" and provide a brief (1–2 line) synopsis.

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