

ADRENOCORTICAL CARCINOMA

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ABSTRACT

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy arising from the adrenal cortex often with unexpected biological behavior. It can occur at any age, with two peaks of incidence: in the first and between the fifth and seventh decades of life. Although ACC are mostly hormonally active, precursors and metabolites may also be produced by dedifferentiated and immature malignant cells. Distinguishing the etiology of an adrenal mass between benign adenomas, which are quite frequent in the general population, and malignant carcinomas with dismal prognosis is challenging. However, recent advances in genomic pathology and staging allow the development of standardization of pathology reporting and refinement of prognostic grouping for planning the treatment of patients with ACC. No single histopathological, as well as no single imaging method, hormonal work-up, or immunohistochemical labelling, can definitively prove the diagnosis of ACC. Over several decades great efforts have been made to find novel reliable and available diagnostic and prognostic factors including steroid metabolome profiling or target gene identification. Preliminary data show that for localized ACC, molecular markers (gene expression, methylation, and chromosome alterations) could predict cancer recurrence. Nevertheless, many of these markers need further

validation and some are difficult to be widely applied in clinical settings. The development of new prognostic tools highlights the need for early identification of high-risk ACC patients who could benefit from individualized management. ACC is frequently diagnosed in advanced stages and therapeutic options are unfortunately limited. The management of patients with ACC requires a multidisciplinary approach. Surgery remains the “gold standard” treatment whereas a number of systemic therapies including chemotherapy is administered in patients with extensive not amenable to surgical resection disease. Recently, immunotherapy in advanced ACC has also been investigated in different studies. However, the reported rates of overall response rate and progression-free survival (PFS) were generally poor. Thus, new biological markers that could predict patient prognosis and provide individualized therapeutic options, especially targeted treatments, are required.

CLINICAL RECOGNITION

Adrenocortical cancer (ACC) is a rare disease with an annual incidence of 0.7-2 cases per million per year and two distinct age distribution peaks, the first occurring in early adulthood and the second between 40-50 years with women being more often affected than men (55-60%) (1,2). Although the great majority

of ACCs are sporadic in origin, they can also develop as part of familial syndromes the most common being the Beckwith-Wiedeman syndrome (11p151 gene, IGF-2 overexpression), the Li-Fraumeni syndrome (TP53 gene germline and somatic mutation), the Lynch syndrome (MSH2, MLH1, MSH6, PMS2, EPCAM genes), the multiple endocrine neoplasia (MEN) 1 (MEN1 gene), familial adenomatous

polyposis (FAP gene, catenin somatic mutations), neurofibromatosis type 1 (NF1 gene) and Carney complex (PRKAR1A gene) syndromes (Table 1) (1-5). In recent years several multi-center studies have shed light on the pathogenesis of ACC but 'multi-omic' multi-studies have recently revealed that only a minority of ACC cases harbor pathogenic driver mutations

Table 1. Clinical and Genetic Features of Familial Syndromes Associated with ACC

Genetic disease Gene and chromosomal involvement	Organ involvement
Beckwith-Wiedemann syndrome CDKN1C mutation KCNQ10T1, H19 (epigenetic defects) 11p15 locus alterations IGF-2 overexpression	Macrosomia, macroglossia, hemihypertrophy (70%), omphalocele, Wilm's tumor, ACC (15-20% adrenocortical tumors)
Li-Fraumeni syndrome P53(17p13)	Soft tissue sarcoma, breast cancer, brain tumors, leukemia, ACC
Multiple Endocrine Neoplasia syndrome 1 Menin (11q13)	Parathyroid, pituitary, pancreatic, bronchial tumors Adrenal cortex tumors (30%, rarely ACC)
Familial Adenomatous polyposis APC (5q12-22)	Multiple adenomatous polyps and cancer colon and rectum Periampullary cancer, thyroid tumors, hepatoblastoma, rarely ACC
SBLA syndrome	Sarcoma, breast and lung cancer, ACC
Neurofibromatosis NF1	Six or more light brown dermatological spots ("café au lait spots) At least two neurofibromas
Carney Complex PRKAR1A not defined	Lentigines, Atrial Myxoma, and Blue Nevi

The clinical features of sporadic ACCs are due to tumor mass effects and spread to surrounding or distant tissues and/or to hormonal hypersecretion. A number of cases (\approx 10-15%) are increasingly diagnosed within the group of incidentally discovered adrenal masses (incidentalomas). However, the

likelihood of an adrenal incidentaloma being an ACC is rather low (2, 6, 7). Approximately 50-60% of ACCs exhibit evidence of hormonal hypersecretion, usually that of combined glucocorticoid and androgen secretion (Table 2). Nearly 30-40% of patients with primary ACC present with a mass-related syndrome

such as abdominal or dorsal pain, a palpable mass, fever of unknown origin, signs of inferior vena cava (IVC) compression, and signs of left-sided portal hypertension. Rarely, complications such as hemorrhage or tumor rupture may also occur.

In biochemical studies, the first step is the measurement of steroid hormones which are initially guided by the clinical presentation. According to the ESMO-EURACAN (European Society for Medical Oncology—the European Reference Network for Rare Adult Solid Cancers) Clinical Practice Guidelines from 2020 in cases of suspected ACC, an extensive steroid hormone work-up is recommended assessing glucocorticoid-, mineralocorticoid-, sex- and precursor-steroids (6-8). For all

adrenal masses, diagnosis of pheochromocytoma should be considered based on clinical presentation and imaging measuring plasma-free or urinary-fractionated metanephrines to avoid intraoperative complications. The European Society of Endocrinology (ESE) and European Network Society of Adrenal Tumors (ENSAT) guidelines on adrenal incidentalomas suggest the measurement of sex steroids and precursors of steroidogenesis using multi-steroid profiling by tandem mass spectrometry in patients in whom based on imaging or clinical features an adrenocortical carcinoma is suspected (9). Urine steroid metabolomics for non-invasive and radiation-free detection of a malignant ‘steroid fingerprint’ in adrenocortical carcinoma patients has been prospectively validated (10).

Table 2. Signs and Symptoms of ACC and Recommended Testing for Confirmation of Hypersecretory Syndromes

Symptoms/Signs	Hormonal testing (ENSAT 2005, ESMO-EURACAN - Clinical Practice Guidelines 2020)
Hypercortisolism Centripetal fat distribution. Skin thinning – striae. Muscle wasting – myopathy. Osteoporosis. Increased blood pressure (BP), Diabetes Mellitus, Psychiatric disturbance, Gonadal dysfunction	Overnight dexamethasone suppression test (1mg) 24-hour free cortisol (urine) Basal ACTH (plasma) Basal cortisol (serum) [for diagnosis minimum 3 out of 4 tests)
Androgen hypersecretion Hirsutism Menstrual irregularity – infertility Virilization (baldness, deepening of the voice, clitoris hypertrophy)	DHEA-S Androstenedione Testosterone 17-hydroxy-progesterone (17OHPG)
Mineralocorticoid hypersecretion Increased BP Hypokalemia	Potassium (serum) Aldosterone to renin ratio
Estrogen hypersecretion Gynecomastia (men) Menorrhagia (post-menopausal women)	17β-estradiol
Non-hypersecretory syndrome	

PATHOPHYSIOLOGY

Although studies of hereditary neoplasia syndromes have revealed various chromosomal abnormalities related to ACC development, the precise genetic alterations involved are still unknown. Most common mutations implicated in sporadic ACC are insulin-like growth factor 2 (IGF2), catenin (CTNNB1 or ZNRF3), and TP53 mutations (1, 4, 11). The Wnt/ β -catenin constitutive activation and insulin growth factor 2 (IGF2 overexpression) are the most important implicated genetic pathways. Germline TP53 mutations and dysregulation of the Gap 2/mitosis transition and the insulin-like growth factor 1 receptor (IGF1R) signaling have also been described. Steroidogenic factor 1 (SF1) plays an important role in adrenal development and is frequently overexpressed in ACC. Recently, ACC global --omics profiling studies revealed frequent detected genetic and epigenetic alterations, including loss of heterozygosity at 17p13, alterations at the 11p15 locus, and mutations in TP53, CTNNB1, ZNRF34, CDKN2A, RB1, MEN1, PRKAR1A, RPL22, TERF2, CCNE1, and NF1 genes. Decreased expression of MLH1, MSH2, MSH6, and/or PMS2 consistent with high microsatellite instability/mismatch repair protein deficiency (MSI-H/MMR-D) status has also been reported (4, 11).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A palpable mass causing abdominal pain in the presence of IVC syndrome is highly suggestive of an ACC. This is substantiated further by the presence of symptoms/signs of combined hormonal secretion (cortisol and androgens), virilizing or rarely feminizing symptoms/signs confirmed with the use of specific endocrine testing (Table 2). As the majority of ACCs are relatively large (size > 8cm, weight >100g) at diagnosis, specific imaging features are used to distinguish them from other adrenal lesions (1, 2, 3). If adrenal imaging indicates an indeterminate mass other parameters should be considered including

tumor size > 4 cm, combined cortisol/androgen hormone excess, rapidly developing symptoms and/rapid tumor growth and/or young age (e.g., < 40 years) at presentation, that all might point to an ACC (1, 2, 3, 5, 7). Other adrenal lesions that need to be considered in the differential diagnosis are myelolipomas, adrenal hemorrhage, lymphoma, adrenal cysts, metastases, and mainly adrenal adenomas, the majority of which have distinctive imaging features. There is no role for biopsy in a patient who is considered suitable for surgery of the adrenal mass (5, 6, 7). Computerized Tomography (CT) imaging of the adrenals is the major tool showing a unilateral nonhomogeneous mass, > 5cm in diameter, with irregular margins, necrosis, and occasionally calcifications. Due to the low-fat content X-Ray density is high (>20 Hounsfield Units, HU); in a series of 51 ACC none had a density of less than 13 Hounsfield Units (HU) (6-8). However, a recent study including almost 100 ACCs showed that increasing the unenhanced CT tumor attenuation threshold to 20 HU from the recommended 10 HU increased specificity for ACC at 80% [95% CI 77.9–82.0] vs. 64% [61.4–66.4] while maintaining sensitivity at 99% [94.4– 100] vs. 100% [96.3–100]; (PPV 19.7%, 16.3–23.5) [EURINE-ACT study] (10). The presence of enlarged aorto-caval lymph nodes, local invasion, or metastatic spread, are highly suggestive of ACC. For 3-6 cm size lesions, measuring CT-related tumoral density before and after contrast administration, and estimating washout percentage can be helpful; less than 50% after 15 minutes, is associated with >90% specificity (7, 8). On Magnetic Resonance Imaging (MRI), ACC appears hypo or isointense in relation to the liver on T1-weighted images and following gadolinium enhancement and chemical shift techniques the diagnostic accuracy obtained can be as high as 85-100% (7, 8). Recently Positron Emission Tomography (PET) imaging with 18F-fluoro-2deoxy- D-glucose (18FDG-PET) has been proposed as possibly the best second-line test to assess indeterminate masses by unenhanced CT exhibiting 95-100% sensitivity and 91-94% specificity that increases further when fused with CT imaging. Furthermore, 18FDG-PET can also

be used as a staging procedure identifying metastatic adrenal disease missed by conventional imaging studies including CT of the chest (7, 8). With the proper implementation of imaging studies there is no need for any adrenal biopsy.

HISTOPATHOLOGICAL DIAGNOSIS

The expression of steroidogenic factor 1(SF1) is a valid marker to document the adrenal origin (distinction of primary adrenocortical tumors and non-adrenocortical tumors) with a sensitivity of 98% and a specificity of 100%. If this marker is not available, a combination of other markers can be used which should include inhibin-alpha, melan-A, and calretinin. The European Network for the Study of Adrenal Tumors (ENSAT) has shown that Ki-67 is the most powerful prognostic marker in both localized and advanced ACC indicative of aggressive behavior and that higher Ki-67 levels are consistently associated with a worse prognosis (2, 6, 12, 13). The Weiss system, based on a combination of nine histological criteria that can be applied on hematoxylin and eosin-stained slides for the distinction of benign and malignant adrenocortical tumors, is the best validated score to distinguish adenomas from ACC although with high inter-observer variability. A reticulin algorithm has been used for the diagnosis of ACC which involves an abnormal/absent reticulin framework and at least one of the three following criteria (tumor necrosis, presence of venous invasion and mitotic rate of >5/50 high power field) (13). Studies have proposed the use of proliferative index (Ki-67 index > 5%) and IGF2 over-expression to confirm the diagnosis of ACC (12, 13). It is important to note that no single microscopic criterion on its own is indicative of malignancy and there is subjective variability in interpretation.

PROGNOSIS

As survival depends on stage at presentation several different classification histopathological systems have evolved with the reported 5-year survival using the

ENSAT system being 82% for stage I, 61% for stage II, 50% for stage III, and 13% for stage IV disease (Table 3) (6-8). Tumor size remains an excellent predictor of malignancy as tumors > 6cm have a 25% chance of being malignant compared to 2% of those with a size < 4cm. As there is no single distinctive histopathological feature indicative of malignancy the Weiss score has been used with a score >3 being suggestive of malignancy and recently Ki-67 labelling index >10%. A relatively new system published by a European group in 2015 is the Helsinki score which relies on mitotic rate, necrosis, and Ki-67 index (3x mitotic count [>5/50 high power fields] + 5x presence of necrosis + Ki-67 proliferative index) of ACC and focus on the predicting diagnosis as well as prognosis of ACC. A Helsinki score >8.5 is associated with metastatic potential and warrants the diagnosis of ACC (13). Altered reticulin pattern, Ki-67% labelling index, and overexpression of p53 protein were found to be useful histopathological markers for distinguishing benign adrenocortical tumors from ACCs; however, only pathological p53 nuclear protein expression was found to reach statistically significant association with poor survival and development of metastases, although in a small series of patients (12).

Most recently, the S-GRAS score was calculated as a sum of the following points: tumor stage (1–2 = 0; 3 = 1; 4 = 2), grade (Ki67 index 0–9% = 0; 10–19% = 1; ≥20% = 2 points), resection status (R0 = 0; RX = 1; R1 = 2; R2 = 3), age (<50 years = 0; ≥50 years = 1), symptoms (no = 0; yes = 1), generating four groups of ACC (0–1, 2–3, 4–5, and 6–9). The prognostic performance of S-GRAS was found superior to tumor stage and Ki67 in operated ACC patients, independently from adjuvant mitotane. S-GRAS score provides a new important guide for personalized management of ACC especially regarding radiological surveillance and adjuvant treatment (14). The COMBI score constitutes an additional predictive score incorporating the DNA-based molecular biomarkers to the S-GRAS including alterations in the Wnt/β-catenin and Rb/p53 pathways and hypermethylation of PAX5 (15).

Table 3. Staging System for ACC Proposed by the International Union against Cancer (WHO 2004) and the European Network for the Study of Adrenal Tumors (ENSAT).

Stage	WHO 2004	ENSAT 2008
I	T1,N0,M0	T1,N0,M0
II	T2,N0,M0	T2,N0,M0
III	T1-2,N1,M0 T3,N0,M0	T1-2,N1,M0
IV	T1-4,N0-1,M1 T3,N1,M0 T4,N0-1,M0	T1-4,N0-1, M1

M0: No distant metastasis, M1: Presence of distant metastasis, N0: No positive lymph nodes, N1: Positive lymph node(s), T1: Tumor ≤ 5 cm, T2: Tumor > 5 cm, T3: Tumor infiltration to surrounding tissue, T4: Tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein.

The median overall survival (OS) of all ACC patients is about 3-4 years (6, 7). The prognosis is, however, relatively heterogeneous. Complete surgical resection provides the only means of cure (6, 7, 16, 17). In addition to radical surgery, disease stage, proliferative activity/tumor grade, and cortisol excess are independent prognostic parameters (6, 7, 16, 17). The five-year survival rate is 60-80% for tumors confined to the adrenal space, 35-50% for locally advanced disease, and significantly lower in cases of metastatic disease ranging from 0% to 28% (6-8). ENSAT staging is considered slightly superior to the Union for International Cancer Control (UICC) staging. Additionally, the association between hypercortisolism and mortality was consistent. As Ki-67 is related to prognosis in both localized and advanced ACC, threshold levels of 10% and 20% have been considered for discriminating low from high Ki-67 labelling index; however, it is not clear whether any single significant threshold can be determined. Patients with stage I-III disease treated with surgical resection had significantly better median OS (63 vs. 8 months; $p=0.001$). In stage IV disease, better median OS occurred in patients treated with surgery (19 vs. 6 months; $p=0.001$), and post-surgical radiation (29 vs. 10 months; $p=0.001$) or chemotherapy (22 vs. 13

months; $p=0.004$) (6-8, 16,17). OS varied with increasing age, higher comorbidity index, grade, and stage of ACC at presentation. There was improved survival with surgical resection of the primary tumor, irrespective of disease stage; post-surgical chemotherapy or radiation was of benefit only in stage IV disease (7, 16). The 5 year-survival of adult patients from multiple datasets with ACC after surgery ranges from 40% to 70%. The estimated five-year OS for patients with ACC in recent cohorts is slightly less than 50% (7, 16). Preliminary data also shows that molecular markers (gene expression, methylation, and chromosome alterations) for localized ACC could predict cancer recurrence (18, 19). Nevertheless, many of these markers need further validation and some are difficult to be widely applied in clinical settings.

The development of genomics has led to a new classification of ACC by two independent international cohorts; one from ENSAT network in Europe (18) and the other from the Cancer Genome Atlas consortium in America, Europe and Australia (19), with two distinct molecular subgroups, C1A and C1B being associated with poor (5-year survival rate of 20%) and good

overall prognosis (5-year survival rate of 91%), respectively. The C1B group is characterized by a low mutation rate, and a very low incidence of mutations of the main driver genes of ACC whereas the C1A group is characterized by high mutation rate and driver gene alterations. This group is further divided into a subgroup of aggressive tumors showing hypermethylation at the level of the CpG islands located in the promoter of genes ("CIMP phenotype"). The prognostic value of paraffin-embedded tumors' transcriptome analysis was also confirmed as an independent prognostic factor in a multivariable model including tumor stage and Ki-67. Oncocytic adrenocortical tumors did not form any specific cluster as oncocytic carcinomas and oncocytic tumors of uncertain malignant potential were all in 'C1B' (20).

THERAPY

The management of patients with ACC requires a multidisciplinary approach with initial complete surgical resection in limited volume disease (stages I, II and occasionally III). Mitotane (1,1-dichloro-2-(ochlorophenyl)- 2-(p-chlorophenyl) ethane [o,p'DDD]) is the only currently available adrenolytic medication achieving an overall response of approximately 30%.

Surgery

Surgery aims to achieve a complete margin negative (R0) resection as patients with an R0 resection have a 5-year survival rate of 40-50% compared to the < 1year survival of those with incomplete resection (7, 17). Patients with stage III tumors and positive lymph nodes can have a 10-year OS rate of up to 40% after complete resection. When a preoperative diagnosis or high level of suspicion of ACC exists, open surgical oncological resection is recommended as locoregional lymph removal might improve diagnostic accuracy and therapeutic outcome. However, the wide range of reported lymph node involvement in ACC (ranging from 4 to 73%) implies that regional lymphadenectomy

is neither formally performed by all surgeons nor accurately assessed or reported by all pathologists (7, 17). Laparoscopic adrenalectomy should be considered for tumors with size up to 6 cm without any evidence of local invasion and open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy and signs of local invasion (9). There is no strong evidence that one of the minimally invasive or open adrenalectomy is superior concerning the time to recurrence and/or survival of patients with ACC, provided that rupture of tumor capsule is excluded. Routine locoregional lymphadenectomy should be performed with adrenalectomy for highly suspected or proven ACC and it should include (as a minimum) the peri-adrenal and renal hilum nodes. Preservation of the tumor capsule is essential whereas involvement of the IVC or renal vein with tumor thrombus is not a contraindication for surgery. However, even following a complete surgical resection, 50-80% of patients develop locoregional or metastatic recurrence. Although such patients may be candidates for aggressive surgical resection, routine debulking is not recommended except for the control of hormonal hypersecretion (6, 7, 17). Ablative therapies particularly targeting hepatic disease are used to decrease tumor load and hypersecretory syndromes. Individualized treatment decisions are made in cases of tumors with extension into large vessels based on a multidisciplinary surgical team. Such tumors should not be regarded as 'unrespectable' until reviewed in an expert center.

Mitotane

Mitotane has traditionally been used for ACCs to obtain a partial or complete response in 33% of cases mainly by metabolic transformation within the tumor and through oxidative damage. Besides its cytotoxic adrenal action mitotane also inhibits steroidogenesis. Adjuvant mitotane treatment is proposed in those patients without macroscopic residual tumor after surgery but who have a perceived high risk of

recurrence (stage III, Ki-67%>10%). However, patients at low/moderate risk of recurrence (stage I-II, R0 resection, and Ki-67 \leq 10%) do not benefit significantly from adjuvant mitotane (ADIUVO trial) (21). An ongoing study, ADIUVO-2, is investigating the effectiveness of mitotane alone compared to mitotane combined with chemotherapy in high-risk ACC patients.

When indicated mitotane should be initiated within six weeks and not later than 3 months post-surgery (7, 17). Adjuvant mitotane should be administered for at least 2 years, but no longer than 5 years. However, the optimal duration of adjuvant mitotane treatment remains unsolved and mainly depends on personal preferences and expertise. According to a recent study, the present findings do not support the concept that extending adjuvant mitotane treatment over two years is beneficial for patients with ACC at low risk of recurrence (22). The tolerability of mitotane may be limited by its side effects mainly nausea, vomiting, neurological (ataxia, lethargy), hepatic and rarely hematological toxicity (7, 22). Measurement of serum mitotane levels, targeting a range of 14-20 mg/l, seems to correlate with a therapeutic response while minimizing toxicity using variable dosing regimens (6-8). Levels above 20 mg/L are linked to a higher risk of central neurological toxicity, though mild symptoms can also occur at lower concentrations. Interestingly, some evidence suggests that steroid secretion inhibition may still occur at lower mitotane levels than 14mg/l, indicating potential therapeutic benefits even outside the standard therapeutic window (23). Additionally, the Ki-67 index, a widely recognized marker of tumor aggressiveness in ACC, is often used to predict disease's progression and the potential effectiveness of mitotane therapy. While elevated Ki-67 levels are typically associated with poorer prognosis, they may also suggest a greater likelihood of response to mitotane when therapeutic concentrations are achieved (24).

Mitotane causes hyperlipidemia and increased hepatic production of hormone-binding globulins (cortisol, sex hormone, thyroid and vitamin D) increasing total hormone concentration while impairing free hormone bioavailability. The induction of hepatic P450-enzymes by mitotane induces the metabolism of steroid compounds requiring high-dose glucocorticoid and mineralocorticoid replacement. Hormonal excess causes significant morbidity in ACC patients. Although mitotane reduces steroidogenesis it has a slow onset of action necessitating the use of other medications targeting adrenal steroidogenesis (ketoconazole, metyrapone, aminoglutethimide, and etomidate). As adrenal insufficiency may occur close supervision is required to titrate adrenal hormonal replacement therapy.

Mitotane remains the primary treatment for ACC, but resistance, both primary and acquired, limits its efficacy. Primary resistance arises from genetic and epigenetic alterations (e.g., TP53, CTNNB1 mutations, gene hypermethylation), the overexpression of drug efflux pumps (e.g., ABCB1), and disruptions in steroidogenic pathways. Acquired resistance develops during treatment, involving pathways like Wnt/ β -catenin, PI3K/AKT/mTOR, and genes such as BCL-2 and TP53. Understanding these mechanisms is essential for developing targeted therapies and improving outcomes (25).

Cytotoxic Chemotherapy

In metastatic ACC or when progression on mitotane, systematic therapy is recommended. Although cisplatin-containing regimens have shown some responses, most studies lack enough power and comparisons between different regimens are only a few. The most encouraging results originate from the combinations of etoposide, doxorubicin, and cisplatin with mitotane (EDP-M) achieving an overall response of 49% of 18 months duration (FIRMA-CT study) (26). This regimen was equally effective as first-line treatment or after failing of the combination of streptozotocin with mitotane and is currently the

preferred scheme. In patients who progress under mitotane monotherapy, EDP treatment is also recommended (7, 26). The combination of gemcitabine with capecitabine is used for patients failing EDP- and for non-responding patients. Targeted therapies with tyrosine kinase inhibitors have been also suggested. In a single-arm, phase 2 trial including 18 patients with advanced ACC treated with monotherapy with cabozantinib, the median progression-free survival (PFS) was 6 months, whereas 72.2% of patients were PFS at 4 months (27). Although initially promising, treatment with IGF-1R antagonists did not prove to be efficacious, suggesting that combination therapies may be the way forward (see below).

Radiation Therapy

Radiotherapy has a role in symptomatic metastatic disease, particularly bone disease with positive responses in up to 50% - 90% of cancer patients. It is a local therapy which is mainly recommended in incomplete resection, recurrent, or metastatic disease. Postoperative adjuvant radiotherapy significantly improved overall survival (OS) and PFS compared with the use of surgery alone in resected localized ACC patients especially those with stage I/II (median Ki-67%=20). However, this finding was mainly in retrospective studies (28).

Immunotherapy

Several Immunotherapy agents have been evaluated in clinical trials for metastatic ACC patients including the immune checkpoint inhibitors (ICIs) pembrolizumab, nivolumab, and avelumab which are monoclonal antibodies directed toward PD-L1, the ligand-binding partner of PD-1, that is expressed on tumor cells. Four ICIs (pembrolizumab, avelumab, nivolumab, and ipilimumab) have investigated the role of immunotherapy in advanced ACC. Despite the different primary endpoints used in these studies, the reported rates of overall response rate and PFS were

generally poor (Table 4) (29-32). Three main potential markers of response to immunotherapy in ACC have been described: Expression of PD-1 and PD-L1, microsatellite instability, and tumor mutational burden (29). PD-1 and PD-L1 are expressed in 26.5% and 24.7% of ACC samples, respectively, with low expression in most tumor samples. In contrast, CTLA-4 expression is observed in 52.5% of ACC samples. Positive PD-1 expression was associated with longer PFS even after considering prognostic factors. In contrast, PD-L1 and CTLA-4 did not correlate with clinical outcomes. Additionally, PD-1 and PD-L1 expression correlated significantly with the amount of CD3+, CD4+, FoxP3+, and CD8+ T cells (33). However, none of these parameters have been validated in prospective studies. Several mechanisms may be responsible for immunotherapy failure, and a greater knowledge of these mechanisms might lead to the development of new strategies to overcome immunotherapy resistance.

Two clinical trials using the PD-1 inhibitor pembrolizumab as monotherapy in ACC have been reported (29, 30). The observed median PFS and OS in the first study were 2.1 and 24.9 months, respectively. Six patients in the study had microsatellite-high and/or mismatch repair deficient status (MSI-H/MMR-D), for which pembrolizumab is an FDA-approved therapy. In the second study, 5 of 14 patients (36%), developed stable disease (SD) at 27 weeks and 2 exhibited a partial response. Nivolumab monotherapy was tested in a phase II trial (31). The best response observed in this trial was 1 out of 10 patients with an unconfirmed partial response and 2 out of 10 patients developing SD (31). Avelumab has been evaluated in a phase 1b clinical trial in patients with metastatic ACC who had progressed after first-line platinum-based therapy (32). In this trial, including 50 patients, 3 patients showed a partial response, and 21 (42%) patients had SD (42%). Median PFS and OS were 2.6 and 10.6 months, respectively. Although no head-to-head study exists to compare ICIs efficacy, a retrospective study of 54 patients with advanced ACC analyzed the

treatment response in different ICIs, demonstrating that after adjustment for concomitant mitotane use, treatment with nivolumab was associated with a lower

risk of progression and death compared to pembrolizumab (34).

Table 4. Studies that have Investigated Immunotherapy in Patients with ACC

Molecule	Phase	Population(n)	Prior systemic treatment	Results
Pembrolizomab 200 mg every 3 w (35 cycles)	II	39	28	PFS=2.1, OS=24.9 ORR (RECIST)=23%
Pembrolizomab 200 mg every 3 w (35 cycles)	II	16	16	SD at 27 w=36%, ORR(RECIST)=14%
Nivolumab 240 mg every 2 w	II	10	10	PFS=1.8, ORR=11%
Avelumab 10 mg/kg every 2 w (±mitotane)	Ib	50	50	PFS=2.6, OS=10.6, ORR=6%
Ipilimumab 1 mg/kg intravenously every 6 weeks with nivolumab 240 mg intravenously every 2 weeks	II	21	21	6-month OS = 76%; the median OS= 15.8 months, ORR=14%
Camrelizumab combined with apatinib	II	21	21	ORR=52%, median PFS=3.3 months, median OS=20.9 months

ORR= objective response rates; PFS= progression-free survival; SD= stable disease; OS= overall survival

Combination therapies with these agents are also evolving either with two different ICIs, most frequently ipilimumab and nivolumab or a combination of ICIs with a different targeted molecule and especially a tyrosine kinase inhibitor (TKI) (35,36). Pembrolizumab along with the VEGF-targeted multi-kinase inhibitor lenvatinib was used in a small retrospective case series including 8 heavily pre-treated patients (the median number of prior lines of systemic therapy was 4) with progressive or metastatic ACC (37). The

median PFS in these patients was 5.5 months (95% CI 1.8–not reached). Two (25%) patients showed a partial response (PR), one (12.5%) patient had stable disease (SD), and five (62.5%) patients developed progressive disease. Other immunotherapies that have been evaluated include the monoclonal antibodies figitumumab and cixutumumab directed against the ACC-expressed insulin-like growth factor 1 (IGF-1) receptor, the recombinant cytotoxin interleukin-13-pseudomonas exotoxin A, and

autologous tumor lysate dendritic cell vaccine (38, 39). All of these agents have shown modest clinical activity. Figitumumab in particular was evaluated in a phase I trial in 14 patients with metastatic ACC. The best response to treatment observed in this trial was SD seen in 8 of 14 patients. Toxicities were generally mild and included hyperglycemia, nausea, fatigue, and anorexia. Similarly, to figitumumab, cixutumumab (IMC-A12) was evaluated in combination with mitotane in a phase II trial as first-line therapy for patients with advanced or metastatic ACC (39). The study was terminated early due to slow accrual and limited efficacy. The recorded PFS was only 6 weeks (range: 2.66–48), and in 20 evaluable patients, the best objective response rates (ORR) were a partial response (PR) in one patient and SD in a further seven. Toxicities observed included grade 4 hyperglycemia and hyponatremia and one grade 5 multiorgan failure.

Immune-Modulators

The potential utility of thalidomide treatment in ACC was evaluated in a retrospective cohort study of the European Networks for the Study of Adrenal Tumors registry (40). In this study, 27 patients with progression on mitotane or metastatic ACC were treated with 50–200 mg thalidomide daily. The best response noted was SD in two patients, while the remaining 25 patients had progressive disease. The median PFS was 11.2 weeks, with a median OS of 36.4 weeks. Thalidomide was generally well tolerated, with fatigue and gastrointestinal upset being the most commonly observed side effects.

Evolving Therapies

Active areas of research in this field include combinations of ICIs, combination TKIs and ICIs, cancer vaccines, and glucocorticoid receptor antagonists combined with ICIs therapies (<http://www.clinicaltrials.gov>). Targeting mTOR pathway alone with everolimus did not produce

significant responses. An extended phase I study of the anti-IGF-1R monoclonal antibody cixutumumab with an mTOR inhibitor showed a partial but short-lived response. Combination treatments such as cabozantinib with atezolizumab in a basket study (CABATEN) or SPENCER study (EO – a novel microbiome-derived therapeutic vaccine with nivolumab) in MSI/PD-L1 negative and low tumor mutational burden tumors have shown a relative response in a subgroup of ACC patients. Other potential targets are antagonists of β -catenin and Wnt signaling pathway and SF-1 inverse agonists. The application of radionuclide therapy using ¹³¹I-metomidate has recently been explored. However, despite recent advances in dysregulated molecular pathways in ACCs, these findings have not yet been translated into meaningful clinical benefits.

FOLLOW-UP

Patients who have undergone a curative resection should be followed up regularly using endocrine markers and abdominal imaging. After complete resection, radiological imaging every 3 months for 2 years and then every 3-6 months for a further 3 years is proposed. However, imaging follow-up beyond 5 years should be adapted in particular cases and be decided by a multidisciplinary team (7). ¹⁸F-FDG-PET should be performed at regular intervals to detect recurrent disease in high-risk patients. Patients on mitotane therapy should be regularly monitored measuring serum mitotane levels ensuring adequate replacement therapy. In case of recurrence not amenable to surgical excision patients should be enrolled in prospective clinical trials.

CONCLUSION

Besides considerable accumulated knowledge on genetic profiling, the pathogenesis of ACC is still not delineated although groups of patients with a worse outcome could be identified. Stage of the disease remains a strong predictor of OS whereas new

evolving biomarkers need to be further validated. Imaging with 18FDGPET is an integral part of the staging procedure but the available medical therapies for patients with advanced disease have not shown a major impact on patients' prognosis. ACC remains a challenging malignancy with limited effective treatment options. Targeted therapies and

immunotherapies, especially in combination regimens, are the subject of continued research. The evolving genomic landscape emphasizes the significance of targeted therapies and the need for further research to identify high-risk patients and formulate efficacious therapies for patients with advanced diseases.

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