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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Management of Adrenocortical Carcinoma

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Abstract

Purpose of Review Adrenocortical carcinoma (ACC) is a rare endocrine malignancy typically with poor prognosis. This review aims to summarize the current knowledge regarding the clinical management of ACC.

Recent Findings Surgery remains the cornerstone for localized ACC management. In more advanced cases, debulking surgery when feasible can help with hormonal control and may allow the initiation of systemic therapy. Over the last few years, our understanding of ACC molecular pathogenesis has expanded with no significant change in treatment options. Platinum-based chemotherapy is the gold standard in metastatic ACC despite suboptimal efficacy. Tyrosine kinase inhibitor use did not result in meaningful benefit in ACC patients. Multiple clinical trials are currently exploring the role of immunotherapy in ACC.

Summary Despite the remarkable improvement in our understanding of the molecular signature and pathways in ACC, this knowledge did not yield a major breakthrough in management of advanced ACC. Multi-institutional and international collaborations are needed to identify promising treatments and new therapeutic targets to improve the care of ACC patients.

Keywords Adrenocortical carcinoma · Mitotane · Targeted therapy · Immunotherapy · Genomic profiling

Introduction

Adrenocortical carcinoma (ACC) is an orphan malignancy with an annual incidence between 0.7 and 2 cases per million population [1, 2]. ACC is more frequent in women (55–60%) with a peak incidence in the fourth and fifth decades of life. ACC is sporadic in majority of cases though it can be a part of hereditary tumor syndromes, such as multiple endocrine neoplasia type 1, Li–Fraumeni, Lynch, familial adenomatous polyposis coli, and Beckwith–Wiedeman syndromes [1].

ACC can be present with signs of excessive adrenal hormone production (60%), pain (30–40%), or incidentally discovered on imaging studies (10–15%) [3]. ACC carries a poor prognosis with overall 5-year survival ranging from 60–80% in patients with ACC stage I to 13% in patients with stage IV disease [4]. The clinical outcomes are heterogeneous given variable tumor biology, disease presentations, and management options. Multiple clinical and pathological factors can influence the prognosis of ACC. Tumor stage at diagnosis is an independent prognostic factor. The combination of tumor size and extension, regional lymph node involvement, and distant metastasis (TNM classification) are key elements in ACC staging. Adrenocortical tumors in children are less aggressive and tend to have better clinical outcomes after complete surgical resection compared to ACC in adults [5, 6]. Even in adults, age was proposed as another variable when categorizing ACC as stage I and II (≤ 55 and > 55 respectively) disease [7]. Cortisol-secreting ACC has worse prognosis with higher recurrence rates and worse survival compared to non-cortisol-producing ACCs [8, 9]. Pathological features such as tumor grade and resection margin status are significant predictors for prognosis. Surgical expertise to achieve complete tumor resection (R0) is critical to improve outcome. The effect of margin

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resection status on prognostic outcomes has been described in few retrospective studies suggesting higher recurrence rate and worse survival in patients with positive margin of resection (R1) [5]. Ki67 proliferation index is a clinically useful pathological marker with strong association with prognosis [10]. In ACC patients (stages I–III) who underwent complete surgical resection, increased Ki67 by 1% was associated with 4% increase in the risk of recurrence. Furthermore, patients with Ki67 of ≥ 20% had overall survival 9.4 months compared to overall survival of 53.2 months in patients with Ki67 < 10% [11••].

ACC Genetics and Mutations

Over the past few years, the advances in genomic methods have expanded our knowledge about gene expression, and genetic and epigenetic alterations at the pan-genomic level in various malignancies. Genomic studies led to the identification of tumor subgroups that have distinct biology and variable outcome allowing for the development of prognostic molecular markers [10]. Approximately 5% of all ACCs occur in patients with Li–Fraumeni syndrome (*TP53*) or Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*). Germline *TP53* mutations are more common in pediatric ACC, as germline *TP53* mutations are frequent and associated with worse prognosis [12]. This highlights the importance of genetic counseling in patients with ACC especially if there is suspicious for hereditary cancer syndrome [13].

Loss-of-function mutations of *TP53* occur in about 20% of adult's ACC [14, 15••] usually associated with loss of heterozygosity (LOH) of the 17p13 region, where *TP53* is located [16]. *CTNNB1* gain-of-function mutations and *ZNRF3* deletions (a negative regulator of Wnt/CTNNB1 and leads to the activation of the Wnt/CTNNB1 pathway) are seen in 20% of ACC [14, 15••].

Genomics studies revealed major differences between aggressive and less aggressive ACCs. Integrated genome analysis identified distinct molecular subgroups of ACC that are associated with different outcomes. The ENSAT network and The Cancer Genome Atlas (TCGA) consortium molecular classification identified two major molecular subgroups, corresponding to ACC of "good" and "bad" prognosis [14, 15••].

The advancement in understanding the molecular biology of ACC has led to the identification of mutation associated with ACC development and factors determining the risks for recurrence and progression, predict tumor aggressiveness, and to identify potentially targetable molecular changes to facilitate personalized management approach [13].

Pathways Involved in ACC

Figure 1 illustrates variable pathways and therapeutic targets in ACC and summarizes the drugs studied or used in ACC management.

i. IGF2 overexpression

The insulin-like growth factor (IGF) system is involved in cancer cell growth [17]. *IGF2* gene is located on 11p15 and *IGF2* gene is maternally imprinted and only expressed from the paternal allele. Over-expression of IGF2 is seen in majority of ACCs and the loss of heterozygosity at the 11p15 region is seen more frequently with ACC than adenomas; it is usually associated with poor outcome [18].

IGF2 regulates the growth and apoptosis when interacts with insulin-like growth factor 1 receptor (IGF1R), the latter is also found to be over-expressed in ACC especially in pediatric cases [19]. Activation of IGF-1R results in stimulation of downstream signaling pathways including the mitogen-activated protein kinase (MAPK) and phosphoinositol-3-kinase (PI3-AKT) pathway, leading to increased cell division and survival [20]. Of note, the genetic alterations of imprinted domains of chromosome 11p15 are implicated in the pathogenesis of Beckwith–Wiedemann syndrome [1].

ii. WNT signaling

The WNT/β-catenin signaling pathway is an important developmental pathway in multiple organ systems, and it is essential in the embryonic development of the adrenal glands [21]. The Wnt/β-catenin signaling pathway is one of the most frequently altered pathways in ACC.

The β-catenin is essential in this signaling pathway, including in cell-cell adhesion, and transcription activation of target genes of the Wnt signaling pathway. Activation of beta-catenin and Wnt signaling pathway is a frequently recognized alteration in both benign and malignant adrenocortical tumors [22]. Activating somatic mutation of the *CTNNB1* in ACC is an independent predictor of less favorable disease-free and overall survival [23].

iii. cMET

Hepatocyte growth factor (HGF) activates cMET in an autocrine and paracrine fashion, leading to enhanced metastatic potential and resistance to therapy in a variety of malignancies including ACC [24••]. HGF stimulates tumor angiogenesis by direct cMET activation, and by increasing the production of angiogenic cytokines, enhancing endothelial cell motility and proliferation [25, 26].

iv. Other

Multiple other pathways involved in cell cycle were identified or currently investigated in ACC [26]. Pan-genomic studies recognized *TP53* as one of ACC driver genes [15••]; therefore, the recovery of p53 function, using MDM2 antagonist, and the reactivation of mutant *TP53* have the potential to be used in ACCs. The Polo-like kinase 1 (PLK-1) is a negative modulator of p53 activity. PLK1 system regulates multiple steps of cell division and DNA stability/repair and is considered a good prognostic marker and candidate for targeted therapy [27].

Hormonal Control in ACC

1. Cushing syndrome

Hypercortisolism in ACC requires immediate and prompt treatment to improve the life-threatening metabolic complications.

a) Mitotane

Mitotane is an adrenolytic drug with an inhibitory effect on adrenal steroidogenesis [28]. It is approved to treat advanced ACC cases and it can be used in combination with other drugs to control cortisol overproduction.

b) Steroidogenesis enzyme blockers

i. Ketoconazole

Ketoconazole inhibits multiple key cytochrome P450 (CYP) enzymes involved in variable steps of steroidogenesis in the adrenal cortex, and can be used in cortisol secreting ACCs. The advantage of using ketoconazole (400–1200 mg/day) is inhibiting androgen production as well. However, routine monitoring of liver function tests is important especially when using mitotane simultaneously as both can be hepatotoxic [29•].

ii. Metyrapone

Metyrapone decreases cortisol synthesis by blocking 11-beta-hydroxylase function [29•]. Adding metyrapone to chemotherapy is often used to rapidly improve the manifestation of Cushing syndrome in patients with cortisol-producing ACC [30].

c) Glucocorticosteroid receptor blocker

Mifepristone

Mifepristone is a glucocorticoid antagonist approved to manage hyperglycemia in the context of Cushing syndrome. Some patients may have worsening hypertension and hypokalemia due to mineralocorticoid receptor activation and may require a concomitant use of high doses of spironolactone or eplerenone to manage hypertension and hypokalemia [31].

2. Hyperaldosteronism

a) Spironolactone and eplerenone

Aldosterone-producing ACCs are rare and cause severe hypertension and marked hypokalemia [32]. They are managed with mineralocorticoid receptor antagonists (spironolactone or eplerenone). It is important to monitor potassium level and renal function during therapy to titrate the dose and avoid electrolyte imbalance [29•]. Spironolactone has anti-androgen effect in addition to the mineralocorticoid receptors blockade.

3. Androgen excess

Androgen-secreting adrenal ACC typically produces androgens, steroid intermediates, and commonly associated with cortisol excess as well. Androgen excess in women negatively influences the quality of life. Patient may have very high levels with serum testosterone, androstendione, and/or DHEA-S. Generally, treatment may involve androgen receptor antagonists, including spironolactone, bicalutamide, or flutamide.

4. Estrogen excess

Estrogen-producing ACCs are exceedingly rare (1–2%). Treatment with estrogen receptor antagonists or aromatase inhibitors can be used [33].

Management of Localized Disease

Surgery

i. Primary resection

Surgical resection carries the best chance for cure in patients with localized ACC [3].

Surgery for ACC should be done by a skilled surgical team, in high-volume centers for adrenalectomies with the goal of a microscopically free margin (R0 resection).

Open adrenalectomy is generally the favored approach in ACC cases, although with careful patient selection, laparoscopic approach has been proposed as an alternative approach in some studies [34, 35], many of which are retrospective in nature.

To date, available evidence suggests higher rates and shorter time to develop loco-regional and peritoneal recurrence, worse

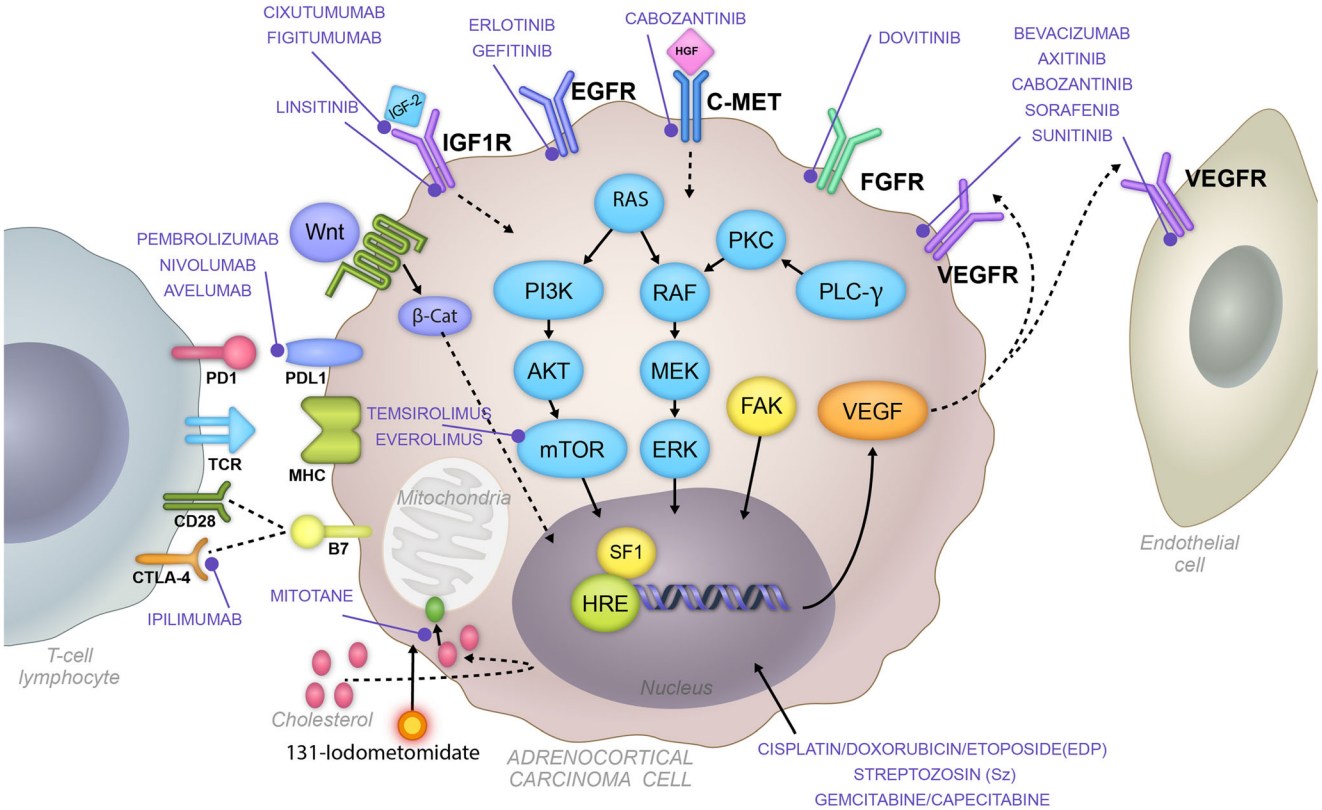

Fig. 1 Different drugs that are currently used or previously studies in ACC with their corresponding cellular targets and pathways

recurrence-free, and overall survival following laparoscopic resection [15••, 36–38]. As such, the long-term advantage of open resection for suspected adrenal masses > 6 cm outweigh the benefits of a minimally invasive approach when ACC is suspected. The lack of randomized controlled trials makes it hard to compare the laparoscopic approach to the open approach in ACC with a diameter of < 6 cm [29•, 39, 40].

There is no agreement regarding the optimal extent of regional lymph node resection during primary resection of ACC [41]. Although the data supporting routine resection of regional lymph nodes are derived from retrospective cohort studies [3], removal of at least 5 regional lymph nodes was associated with reductions in the risk of tumor recurrence and disease-related mortality [42, 43].

Neoadjuvant Approach

Limited data are available regarding the use of neoadjuvant systemic therapy in ACC. Neoadjuvant chemotherapy improved the outcomes in 15 patients with borderline resectable ACC (defined as having oligometastases, reduced performance status, or requiring multi-organ resection) and these patients had similar overall survival and disease-free survival compared to 38 patients with more localized ACC who were managed with surgical resection alone [44].

Adjuvant Therapy

There is lower risk of tumor recurrence when patients with ACC undergo surgery in high-volume center and by experienced surgeons [45]; however, the risk of recurrence remains high approaching 60–70%, requiring the use of adjuvant therapies after surgical resection.

i. Mitotane

The routine use of adjuvant mitotane to improve recurrent-free survival in ACC is controversial and mostly based on retrospective evidence of improved recurrence-free and overall survivals in patients who received adjuvant mitotane [46, 47•].

Currently, an international, multicenter, prospective, randomized trial (ADIUVO trial) is enrolling low-risk ACC patients (defined as stages I–III after complete surgical resection with Ki67 < 10%) to establish the role of adjuvant mitotane in low-risk ACC (ClinicalTrials.gov Identifier: NCT00777244).

ii. Mitotane with chemotherapy

Mitotane is a fat-soluble oral agent that requires few months of therapy to reach what is considered a therapeutic oncological level. Few high-volume centers offer adjuvant platinum-based chemotherapy with mitotane in the first few

months after surgery in high-risk ACC patients. There is an ongoing international, multicenter trial (ADIUVO-2) comparing the two practices of using mitotane alone compared to mitotane with cisplatin and etoposide as adjuvant therapy to treat patient with ACC who are at high risk of recurrence (stages I–III with Ki67 ≥ 10%) (Clinicaltrials.gov ID NCT03583710).

iii. Radiation therapy

The use of adjuvant radiotherapy in ACC relies on retrospective studies. In a recent meta-analysis of multiple cohort studies, there was reduced likelihood of recurrence and prolonged time to recurrence when adjuvant radiation was used in ACC but there was no evidence to support improved overall survival in those patients [48]. More recent data showed survival benefit with radiation use in patients with non-metastatic ACCs who had positive resection margins (R1) [49••].

Management of Recurrent/Metastatic Disease

Surgery

There is limited data to support the efficacy of surgical resection in metastatic disease. Despite the low likelihood of complete tumor removal in advanced ACC, surgery is still an important therapeutic option in metastatic ACC when feasible. Surgery is associated with better survival, even in advanced ACC [50]. Salvage resection or metastasectomy can be offered especially with metastases in single organ [51].

The European Society of Endocrine Surgeons (ESES) and ENSAT recommendations did not support palliative or debulking surgery for metastatic ACC due to insufficient evidence [52]; however, a recent study suggested that surgery of the primary site improved overall and cancer-specific survival in metastatic ACC patients [53]. Of note, phase I and II trials using heated intraperitoneal chemotherapy with cisplatin have been done in some tumors that spread primarily to the peritoneal lining of the abdomen. This encouraged the launching of phase II clinical trial of using heated intraperitoneal peritoneal chemotherapy (HIPEC) after surgical debulking of ACCs. The purpose of this trial is to determine if surgical approach followed by intraperitoneal administration of heated cisplatin when tumor volume is minimal can favorably influence the progression-free survival in patients with ACC (ClinicalTrials.gov Identifier: NCT03127774).

Mitotane

Mitotane is a key therapy for inoperable or metastatic ACC. Mitotane monotherapy is usually given in cases of low tumor burden or less aggressive disease, but need to be combined with cytotoxic chemotherapy in more aggressive disease or advanced ACC as mitotane monotherapy might not be enough [54]. Mitotane therapeutic level target is 14–20 mg/L. Mitotane should be given under the supervision of experienced team, as mitotane is associated with adrenal insufficiency and often requires higher glucocorticosteroid replacement compared to other patients with adrenal insufficiency from other causes. Moreover, mitotane is a strong cytochrome P450-3A4 (CYP3A4) inducer which leads to significant drug-drug interactions leading to the inactivation of other ongoing treatments such as antimicrobials, anti-emetics, anti-depressants, and other drugs that are usually metabolized through CYP3A4 [55].

Chemotherapy

Etoposide, doxorubicin, and cisplatin (EDP)-mitotane regimen is considered the standard chemotherapy in advanced ACC. EDP-mitotane use was associated with longer progression-free survival (5.5 months) compared to the combination of streptozocin plus mitotane that had progression-free survival of 2.1 months [56]. However, up to 58% of patients receiving EDP-M had serious adverse events compared to 41% in the mitotane plus streptozocin arm [56].

GEM-based chemotherapy (gemcitabine + capecitabine) is well-tolerated, but modestly active, regimen against advanced ACC. This can be used with or without mitotane [57•].

Targeted Therapy

Several kinase inhibitors have been investigated in advanced ACC but the results were largely discouraging. However, the efficacy might have been influenced by increased kinase inhibitor use with mitotane-induced CYP3A4 activity. To date, no specific tyrosine kinase inhibitor is approved in treating advanced ACC [29•].

1. IGF1R inhibitors

a) Monoclonal antibodies

i. Cixutumumab

Cixutumumab is a recombinant human monoclonal antibody against IGF-1R. Its efficacy against ACC was studied in combination with mitotane in 20 patients with unresectable or metastatic ACC; however, this combination did not show encouraging outcomes [58].

Cixutumumab in combination with temsirolimus, an mTOR inhibitor, was generally tolerated and about 40% of patients had stable disease more than 6 months despite failing multiple lines of therapy before receiving this combination [59].

ii. Figitumumab

The anti-IGF-1R monoclonal antibody figitumumab was studied in 14 patients with metastatic ACC. Eight patients had stable disease without confirmed responses by RECIST criteria [60].

b) Linsitinib

Linsitinib is an oral inhibitor of the IGF-1R and insulin receptor that showed partial response in two of 15 patients with ACC in early studies [61]. However, linsitinib did not improve progression-free or overall survival when studied in double-blind placebo controlled phase III clinical trial [62••].

2. VEGFR inhibitors

There is increased expression of mediators of tumor angiogenesis and proliferation such as vascular endothelial growth factor (VEGF), VEGF receptor 2 (VEGFR2), and heparanase-1 (HPA-1) in ACC [63]. As such, anti-angiogenic agents thought to have promising role in the treatment of ACC.

a) Bevazicumab

Bevacizumab, a monoclonal antibody, binds to VEGF and block the interaction with VEGF receptors [64]. The combination of metronomic capecitabine and bevacizumab was studied in advanced ACC who progressed on prior mitotane and other lines of chemotherapy without clear evidence of clinical benefit [65].

b) Multi-kinase inhibitors

i. Sorafenib

Sorafenib is a multiple kinase inhibitor that inhibits VEGFR2–3, platelet-derived growth factor (PDGFR), and the enzyme RAF-1. Its effectiveness was described in some case reports [66]; however, this was not true when it was studied in combination with metronomic paclitaxel in 25 patients with metastatic ACC who had progressed on mitotane and other chemotherapy regimen and the trial was prematurely stopped due to early disease progression [67].

ii. Sunitinib

Sunitinib is an oral multi-kinase inhibitor which inhibits VEGFR1-2, c-KIT, Fms-like tyrosine kinase 3, and PDGFR. In a phase II study, single-agent sunitinib was given to patients with advanced ACC, only 5/35 patients had stable disease with progression-free survival of 5.6 to 11.2 months and overall survival of 14.0 to 35.5 months, while 24/35 had progressive disease or died (6/35). However, as mitotane is known to induce cytochrome CYP3A4, its concomitant or prior use with sunitinib may have influenced the results of this study. Mitotane use increases sunitinib clearance as suggested by having very low serum levels of sunitinib and its active metabolites [68].

iii. Dovitinib

Dovitinib, an oral multi-kinase inhibitor, targets fibroblast growth factor receptors, platelet-derived growth factor receptors, and VEGF receptors. Evaluation of this drug efficacy in phase II trial showed no objective response. However, stable disease was seen in 23% of the patients for more than 6 months [69].

iv. Axitinib

Axitinib, selective inhibitor of VGEFRs 1-3, was studied in a phase II trial in 13 patients with metastatic ACC previously treated with chemotherapy with or without mitotane. There were no objective responses during therapy as defined by RECIST criteria; however, stable disease of more than 3 months was seen in 8 patients. The median progression-free and overall survival durations were 5.48 and 26.92 months, respectively. The survival duration thought to reflect patients who had indolent nature of the disease as median overall survival was 3 years prior to study enrollment [70].

v. Cabozantinib

Cabozantinib is a multi-kinase inhibitor including cMET that reduced ACC tumor growth in vitro and in mice xenografts [24••].

There is an ongoing phase II trial of using cabozantinib in patients with locally advanced or metastatic unresectable ACC (Clinicaltrials.gov ID: NCT03370718).

3. EGFR inhibitors

Epidermal growth factor receptor (EGFR) is significantly over-expressed in ACC [71].

EGFR inhibitors gefitinib and erlotinib were studied in a phase II trial without evidence to support good clinical efficacy in ACC [72, 73].

4. mTOR inhibitors

The mTOR pathways play a role in the regulation of cell proliferation, survival, angiogenesis, and resistance to antitumor treatments via the phosphoinositide 3-kinase/protein kinase B signaling pathway [20]; mTOR inhibitors inhibited cell proliferation and cortisol production in ACC cells [74].

The combination of an mTOR inhibitor (temsirolimus), and an immunomodulatory agent (lenalidomide), was studied in a phase I study of patients with advanced cancers, including 3 patients with ACC. Only one of three patients with ACC had stable disease for at least 6 months [75]. Temsirolimus, in combination with cixutumumab, was discussed above.

A phase I study of pazopanib and everolimus in patients with advanced solid tumors included one patient with ACC. This single patient had a stable disease for 13 months [76].

5. Wnt signaling inhibitors

The Wnt/β-catenin signaling pathway is an important developmental pathway in many organs, including the adrenal gland. Targeting this pathway showed promising results in multiple malignant tumors [77].

Genetic alteration involving deletions and point mutations in *CTNNB1* and activation of Wnt/β-catenin occurs frequently in ACCs. Alterations in Wnt/β-catenin signaling pathways have a negative effect on overall survival of patients with ACC [78].

In vitro studies to block the Wnt/b-catenin signaling in ACC cell line have shown increased apoptosis and impairment of adrenal steroidogenesis [79]. However, it is important to note that 27% of benign adrenocortical tumors have β-catenin mutations [80]; therefore, the clinical use of Wnt inhibitors to target this pathway will be challenging.

Immunotherapy and Immune Checkpoint Inhibitors

Immunotherapy has revolutionized cancer therapy. The antineoplastic activity of immune checkpoint inhibitors such anti-CTLA-4, anti-programmed death-1 (anti-PD-1), and anti-PD-ligand-1 (PD-L1) antibodies in different solid malignancies has sparked interest to explore their potential efficacy in ACC [20].

PD-L1 expression was assessed through immunohistochemistry in patients with surgically treated ACC with no evidence of correlation between PD-L1 expression and clinical parameters for survival [81•]. Moreover, IL-13Rα2 is overexpressed in ACC cell; IL-13-PE is a recombinant cytotoxin consisting of human interleukin-13 (IL-13) and a truncated form of pseudomonas exotoxin A (PE) [82].

Multiple ongoing clinical trials are currently evaluating the role of immune checkpoint inhibitors in ACC:

IL-13-PE

In a phase I trial using intravenous infusion of IL-13-PE in ACC patients with IL-13Rα2 expression, stable disease was observed in 1/5 patients who were treated at maximum-tolerated dose with progression times ranging from 1 to 5.5 months. The drug efficacy might have been limited by the development of neutralizing antibodies in 67% of the patients [83].

Ipilimumab

Two phase II clinical trials are ongoing to test the safety and effectiveness of ipilimumab (anti-CTLA-4 antibody) in combination with nivolumab (anti-PD1 antibody) in patients with rare genitourinary malignancies including ACC (ClinicalTrials.gov Identifier: NCT03333616) and (Clinicaltrials.gov ID: NCT02834013).

Pembrolizumab

Pembrolizumab is a humanized anti-PD1 antibody. Two pembrolizumab-based therapeutic trials are ongoing in ACC (ClinicalTrials.gov Identifiers: NCT02673333 and NCT02721732).

Avelumab

Avelumab is monoclonal antibody that targets PD-L1. In phase 1b expansion cohort, 50 patients with metastatic ACC who were previously treated with platinum-based therapy received avelumab every 2 weeks. Mitotane was continued in 50% of patients but mitotane levels were not recorded during the study. Avelumab showed clinical activity and a manageable safety profile. Twenty-one patients (42.0%) had stable disease as best response with median progression-free survival of 2.6 months, and median overall survival of 10.6 months. The 1-year overall survival rate was 43.4% [84•].

Nivolumab

Nivolumab is a monoclonal antibody that targets PD-1 receptor on T cells. In a phase II study, nivolumab was used in 7 patients with metastatic ACC who failed other treatments. Nivolumab use was associated with a median time to progression of 8 weeks, 5 of those patients has progressed and 2 were pending evaluation at the time of the study report [85].

Radiopharmaceuticals

^{131}Iiodometomidate

About 30% of ACCs have significant uptake of iodometomidate in metastatic ACC [86]. Labeling of iodometomidate with ^{131}I offers targeted radionuclide therapy for advanced ACC. In 11 patients with advanced ACC who had high [^{123}I] iodometomidate on diagnostic scans, using

[^{131}I] iodometomidate resulted in partial response in 1 patient, stable disease in 5 patients, and progressive disease in 4 patients while 1 patient died 11 days after treatment but the death was not related to treatment. [^{131}I] iodometomidate therapy was associated with progression-free survival of 14 months (range, 5–33) and the main toxicities included adrenal insufficiency and transient bone marrow depression [87, 88].

Radiation Therapy

Radiotherapy is traditionally used as a palliative therapy especially in symptomatic bone, brain, or inferior vena cava involvement [89]. Radiotherapy could be used as an alternative to systemic therapy or surgery in highly selected patients with oligo-metastases who are not good candidates for surgery or systemic therapy.

Radiofrequency Ablation

Percutaneous image-guided radiofrequency ablation (RFA) is appealing as minimally invasive, locally effective treatment choice, in patients who are not good candidates for reoperation [90].

Available data on loco-regional therapeutic options are generally sparse. However, evidence has shown that RFA can potentially result in effective, short-term local control of primary ACC when tumors are less than 5 cm in size, and close to sensitive tissues or large blood vessels. A small case series of 15 ACC recurrences demonstrated that RFA was well tolerated. Decrease in tumor size or loss of enhancement on imaging was seen in 53% of patients. When the tumor size was smaller than 5 cm, up to 67% had a complete ablation [91].

With advanced technology nowadays, RFA may have a role in treating recurrent ACC in selected patients.

Supportive Therapy

Anti-resorptive Therapy for Bone Metastasis

Bone metastasis is associated with poor quality of life in cancer patients due to bone pain and increased risk of adverse skeletal-related events such as hypercalcemia and pathological [29•].

No evidence are available to support the use of anti-resorptive therapy in metastatic ACC compared to other primary malignancy such as breast, prostate, and lung where bone strengthening therapy demonstrated efficacy in the prevention of skeletal-related events in patients with bone metastasis. However, the current European Society of Endocrinology endorse the administration of denosumab or bisphosphonate therapy in oncological doses along with calcium and vitamin D supplementation in patients with ACC and metastatic bone disease, or in anti-osteoporotic doses, if ACC is associated with glucocorticoid-excess which is known to increase the risk of osteoporotic fractures [29•].

Conclusion

ACC management remains challenging considering the heterogeneous and often unpredictable nature of this disease. The advances in molecular analysis provided plethora of prognostic factors and broadened our understanding about the underlying molecular changes in ACC. Unfortunately, the advanced molecular understanding of ACC has not yielded a major therapeutic breakthrough yet and EDP-M remains the main systemic therapy option for many patients. Ongoing international collaborations carry hope to identify better treatments compared to the currently used options.

Compliance with Ethical Standards

Conflict of Interest Sina Jasim declares that she has no conflict of interest. Mouhammed Amir Habra has received research funding from Exelixis and has received compensation from HRA Pharma and Eisai for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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