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Adrenocortical Carcinoma: The Management of Metastatic Disease

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Abstract

Adrenocortical cancer is a rare malignancy. While surgery is the cornerstone of the management of localized disease, metastatic disease is hard to treat. Cytotoxic chemotherapy and mitotane have been utilized with a variable degree of benefit and few long-term responses. A growing understanding of the molecular pathogenesis of this malignancy as well as multidisciplinary and multi-institutional collaborative efforts will result in better defined targets and subsequently, effective novel therapies.

Keywords

Adrenocortical carcinoma; therapeutics; targeted therapies; metastatic disease

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy of the adrenal cortex with an annual US incidence around 1–2 cases per million population^{1,2}. Notably, given reliance of incidence data on NCI surveys from the 1970's as well as the challenge in proper histopathologic diagnosis, the true incidence may be underestimated.

ACC can occur at any age, but there is a bimodal distribution with a first peak at childhood (1–6 years old) and the second peak in the fourth to fifth decade of life³. The Surveillance Epidemiology End Results (SEER) data reports an incidence of 0.3 per million in children younger than 15 years. Notably, there is an up to 18-fold higher incidence of cases in children in southern Brazil due to environmental and genetic risk factors which have been

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Disclosure

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identified⁴. In this population, germline mutations of the *TP53* tumor suppressor gene (R337H) have been detected in 34% of the patients⁵. In addition to the above demographics, women have a higher incidence compared to men of about 2:1 with studies showing proliferative effects of estrogen on ACC cells, although not establishing this as a clear cause for the higher female incidence^{6,7}.

Sporadic ACC is a heterogeneous neoplasm with a poorly understood molecular pathogenesis⁸. The relationship between ACC tumorigenesis and familial hereditary syndromes has provided some insights into the molecular biology of this disease (Table 1)⁹. Chromosome imbalances (losses and gains) in specific loci of DNA have been reported with impact on several genes such as *TP53*, insulin-like growth factor type II (*IGF-2*), steroidogenic factor 1 (*SFI*) and β -catenin. Given their roles, these genes have been identified as potential candidates for targeted therapies^{10–12}.

Overall, ACC carries a poor prognosis with the most important prognostic factors being the tumor stage at time of diagnosis. Unfortunately, with the absence of specific cancer-related early symptoms about 70% of patients are diagnosed with stage III or IV disease. In a European series of patients, the 5-yr survival rates were 60% for stage I, 58% for stage II, 24% for stage III, and 0% for stage IV. Importantly, the median survival for metastatic disease (stage IV) at the time of diagnosis is less than a year¹³.

ACC management often requires a multidisciplinary approach, frequently involving a medical oncologist, an endocrine surgeon, an endocrinologist and several other disciplines. Surgical resection remains the cornerstone of the treatment and represents the only curative option for patients with early stage ACC. However, around 80% of these patients will present local or distant recurrence after a complete resection¹⁴. With regard to recurrent or advanced disease, ACC is modestly responsive to standard cytotoxic chemotherapies, although various combinations have shown clear palliative benefit. Radiation and ablative techniques have been utilized with variable benefit depending on the clinical scenario.

The above realities highlight the fact that effective systemic treatments for advanced disease are lacking. The pipeline for novel drug development and testing in clinical trials has been limited. The goal of this manuscript is to review the advances in the therapy of advanced ACC. With the recent evolution of new technologies producing genetic data and the molecular characterization of multiple solid tumors described by The Cancer Genome Atlas, we will also focus on the potential of targeted signaling pathways and personalized therapies.

2. Evidence Acquisition

A systematic review of the MEDLINE databases was performed on September 2013. The search was conducted using the keywords “general surgery”, “therapeutics”, “mitotane”, “radiotherapy”, “biological markers”, “oncogenes”, “tumor suppressor genes”, “drug therapy” and “adrenocortical carcinoma”. In total, 266 abstracts were identified. Articles about advanced disease were manually selected. Full text of potentially relevant studies (97 articles) were carefully examined by the authors and considered for analysis. Review articles were also analyzed. We searched abstracts and virtual meeting presentations from the

American Society of Clinical Oncology (ASCO) (<http://www.asco.org/ASCO>) and Endocrine Society conferences from 2004 to 2013 Pertinent material was retrieved and critically evaluated (Figure 1).

3. Evidence Synthesis

3.1. Surgery

In patients with advanced disease, surgery remains an important consideration when complete resection of the primary tumor and all metastases is feasible. In contrast, cytoreductive debulking surgery should be carried out in selected patients with severe hormone excess that is refractory to medical management^{15,16}.

Despite aggressive surgical intervention, local recurrences are frequent. Salvage resections may be considered especially if more than 12 months have been elapsed from the initial surgical treatment and single site of metastasis^{17–20}. However, data on the effectiveness of surgery in the management of recurrent disease are still lacking. Erdogan and colleagues suggested two major predictors for clinical outcome after first recurrence, namely time to first recurrence over 12 months and resectability of tumor lesions (R0-resection)²¹.

A recently published study reported that, in selected patients with ACC and liver metastases, major liver metastectomy was associated with long-term survival, with a 5 year-survival of 39%. However, cure is generally not achievable²².

Based on data from the adjuvant setting, we suggest the application of “adjuvant” treatment concepts as soon as complete surgical resection of metastatic disease has been performed.

3.2. Radiation Therapy

Radiation therapy has been labeled as ineffective in adjuvant or primary treatments for ACC²³. However, increasing evidence supports the rational that ACC is not a radiotherapy-resistant tumor and palliative radiotherapy has been successfully used to treat symptomatic metastatic lesions^{24,25}.

We identified 9 articles reporting palliative radiation therapy for advanced ACC with administered radiation doses ranging from 10 Gy to 60 Gy^{26–28}. Response criteria included mainly pain relief, and was obtained in about 72% of the cases^{20,27–30}. In addition, radiotherapy is effective for improving neurologic symptoms from brain metastasis³¹. It remains an individual decision whether a patient with widespread metastasis and a very limited life expectancy should receive radiotherapy. Non specific recommendation exists for cerebral metastasis, vena cava obstruction and bone metastasis with spinal cord compression³¹.

Interestingly, pre-clinical models suggest that mitotane may function as a radiosensitizer³². This is an important question which requires further investigation given the implications across a number of clinical scenarios like the adjuvant setting, which are beyond the scope of this paper.

3.3. Other Interventional Therapies

Local therapies as chemoembolization or radiofrequency ablation have also shown to play a palliative role in metastatic disease. Percutaneous radiofrequency ablation may provide short-term local control in unresectable primary tumors, particularly for those with less than 5 cm in diameter^{33,34}. In addition, transcatheter arterial chemoembolization may be considered as part of the therapeutic arsenal to treat liver metastasis from ACC³⁵, especially in cases in which the diameter of the target metastasis is 3 cm or smaller³⁶. Similar to considerations for metastatectomy, an individualized decision is required for each patient based on both disease- and patient-specific characteristics.

3.4. Systemic Therapies

The most frequently used systemic drugs in the advanced disease include mitotane, cisplatin and etoposide used alone or in combination with other agents³⁷. Fareau and coworkers described retrospectively the experience of one institution over 20 years with different first line chemotherapies including mitotane, cisplatin, etoposide, streptozocin, doxorubicin, paclitaxel, gemcitabine, cyclophosphamide and ifosfamide. No overall survival (OS) advantage was observed for any single agent or combination over others³⁸. Systemic chemotherapy will be reviewed in more details later.

3.4.1. Adrenolytics—Mitotane is an adrenal-specific cytotoxic agent, which can also lead to necrosis of the adrenal gland. It plays an important role in palliation of effects of hypercortisolism from hormonally active ACC. Evidence for use of mitotane as the only approved drug for advanced ACC is based on retrospective series of data as opposed to any prospective, randomized controlled trials. Mitotane is considered one of the most active agents in ACC with response rates ranging from 13 to 31%³⁹. However, complete responses rarely occur¹⁵. In terms of overall survival, four studies concluded that mitotane treatment does not increase the survival rate whereas five found an increase in the survival rate^{7,20,39–45}. It is important to note that mitotane therapy may prolong recurrence-free survival when used as an adjuvant treatment for patients who have undergone radical resection of their primary tumor⁴⁶.

The optimal dosing regimens of mitotane are not largely known. Among the studies in which survival influence of mitotane was addressed, three studies reported superior clinical benefits in patients with plasma levels above 14mg/l. Plasma levels of 14 mg/l or greater have produced a significant response rate whereas only occasional responses have been described when plasma mitotane levels remain below this threshold^{39,47,48}. In addition, significant toxicities have been reported when plasma levels exceed 20 mg/l^{49,50}. Therefore, we recommend to start mitotane at 0.5g daily and increase 0.5g weekly according to tolerance targeting mitotane blood level between 14–20 mg/l^{51,52}. The narrow therapeutic window can be difficult to achieve, and severe side effects are generally dose limiting during the treatment. It is important to note that mitotane itself is not active, rather must be metabolized to be transformed into therapeutic metabolites that are capable of adrenolysis⁵³. Because of this unique characteristic, measuring circulating mitotane levels serve as a surrogate for the active metabolites. Some individuals are clearly capable of metabolizing mitotane into its active constituents more readily than others, as evidenced by therapeutic

and toxic effects occurring in some individuals at very low mitotane doses, while much higher doses in others.

Although mitotane is metabolized and cleared primarily by the liver, one of its most profound and dynamic influences is accelerating CYP3A4 activity. Since the vast majority of medications are metabolized or altered by hepatic CYP3A4, mitotane therefore has a significant impact on drug metabolism and drug-drug interactions. A few notable examples of mitotane-induced hepatic CYP3A4 effects include: 1) glucocorticoid insufficiency; 2) hyperlipidemia and HMG-CoA inhibitor metabolism; 3) and increased macrolide metabolism.

Almost all patients on mitotane agent will develop some form of glucocorticoid (and occasional mineralocorticoid) insufficiency, and therefore require adrenal supplementation. This is the result of dual mitotane effects: direct adrenolysis and accelerated hepatic metabolism of adrenal steroids by CYP3A4. In addition, mitotane increase hepatic production of globulins (such as cortisol binding globulin [CBG] and thyroid binding globulin [TBG]), thereby further lowering the free concentrations of circulating cortisol.

Patients on mitotane should be empirically treated with low dose hydrocortisone to prevent adrenal crises, and treating physicians must be aware that patients may require increasing doses of glucocorticoids (well into the supraphysiologic range) to achieve normal adrenal replacement. Patients on full dose mitotane therapy often need 50mg of hydrocortisone daily, or more, to treat the vague and diffuse symptoms of cortisol insufficiency. Our usual approach is to start by hydrocortisone 20 mg in the morning and 10 mg in the afternoon when patients achieve a daily mitotane intake of 2 grams. Measuring ACTH, 24h urine free cortisol, and urinary cortisol, and plasma renin activity, in addition to detailed history, can help guide adrenal steroid replacement.

Mitotane induces hypercholesterolemia (primary high LDL and triglycerides) via unclear mechanisms. Mitotane also accelerates the clearance of simvastatin and atorvastatin which are metabolized by CYP3A4; therefore, when statins are used, pravastatin or rosuvastatin are preferred for maximal effectiveness. Lastly, mitotane-induced CYP3A4 activity prevents adequate levels of macrolide antibiotics; therefore, when antibiotics of this class are indicated, consideration for using levofloxacin or ciprofloxacin should be made.

Other toxicities experienced with mitotane can vary and need active medical monitoring and intervention. Local gastrointestinal discomfort (i.e. nausea, vomiting or diarrhea), fatigue, and central nervous system toxicities (memory loss, ataxia, dizziness) are common. Mitotane can cause a central hypothyroidism and inhibits the conversion of testosterone to dihydrotestosterone⁵⁴; both of these effects can further compound fatigue and systemic symptoms^{55,56}.

Patients on mitotane should initially undergo laboratory evaluation every 4–8 weeks to monitor: electrolytes, kidney and liver function tests. Free thyroxine levels, testosterone in men, and lipid profile should be assessed every 3–4 months. Plasma renin activity, ACTH, and a 24 hours urine collection for free cortisol can help assess the adequacy of adrenal steroid replacement, and can be considered at every visit or if suggestive symptoms.

3.4.2. Cytotoxic Chemotherapy

3.4.2.1. First-Line: Chemotherapy with single agents has produced disappointing results and low response rates⁵⁷. With the exception of one large randomized clinical trial, combination of cytotoxic agents to attack ACC was exclusively investigated in retrospective series or small phase II studies (Table 2).

Platinum-based chemotherapies achieve responses ranging from 11 to 48% and the best results may be explained by patient selection⁵⁸. A small phase II study conducted by the Southwest Oncology Group Study (SWOG) enrolled 47 patients with advanced disease to evaluate first-line treatment with cisplatin and etoposide followed by mitotane at disease progression. This trial reported 11% of patients with objective response and confirmed some activity with this strategy⁵⁹.

The best outcomes in advanced ACC were achieved by etoposide, doxorubicin, and cisplatin (EDP) or streptozotocin, both in combination with mitotane. The first combination was studied in a phase II trial with 28 patients in which complete response (CR) was reported in two patients and partial response (PR) in 13, for an overall response rate of 53.5%⁶⁰. The second regimen was evaluated by Khan and colleagues in 22 patients with advanced ACC. In this phase II study, CR or PR were obtained in 36.4% of patients treated with streptozotocin combined with mitotane (SM)⁶¹. These results provided the rationale for an international initiative establishing the standard first-line treatment in advanced ACC.

The first international randomized trial in locally advanced and metastatic adrenocortical carcinoma treatment (FIRM-ACT) compared these two successful regimens in the first-line to establish a standard of care in this setting. In this large collaborative effort, 304 patients were enrolled to receive mitotane plus a combination of etoposide, doxorubicin and cisplatin (M/EDP) or streptozocin plus mitotane (SM). The progression-free survival (PFS) was significantly longer in the M/EDP than SM groups (5.0 vs 2.1 months). The response rate was also higher in the M/EDP group (23.2% vs 9.2%) and the toxicity profile was similar. There was no significant difference in OS (14.8 vs 12.0 months). Importantly, the study design included cross-over at treatment failure and the M/EDP group included many patients who had first-line SM failures. These findings may explain the similar OS in the two groups. The quality of life and rate of serious adverse events were comparable between the two groups. Despite no differences in OS were found, this study provides the most robust evidence for the systemic treatment of advanced ACC⁶².

Most recently, a phase II study enrolled 19 patients with advanced ACC to demonstrate the efficacy of cisplatin plus docetaxel. The median PFS was 3 months. Therefore, the combination of different agents, such as taxanes, did not appear to improve the clinical outcome when compared with other combinations usually used to treat this disease⁶³.

3.4.2.2. Second-line: Studies evaluating the impact of chemotherapies in the second-line are limited and have described disappointing results. A secondary endpoint of the FIRM-ACT trial was to evaluate the efficacy of both regimens in the second-line. The PFS was 2.2 months among the 84 patients who were treated with second-line SM. Among 101 patients

who are treated with M/EDP in this setting the PFS was 5.6 months. These findings reassure the higher antitumor efficacy of M/EDP as both first- and second-line therapy⁶².

A phase II trial addressed the role of gemcitabine plus metronomic 5-Fluorouracil or capecitabine in heavily pretreated patients with advanced ACC. One of the 28 patients (3.5%) presented complete response and other one patient a partial regression. Notably, 11 patients (39.3%) achieved stable disease (SD). Therefore, this treatment scheme may potentially delay the disease progression in pretreated advanced ACC⁵⁸. One explanation for these results is the concept of metronomic therapy. The administration of low doses of chemotherapy on a frequent or continuous schedule may have both antiangiogenic and immunomodulatory effects resulting in disease stabilization in tumors that had become resistant to conventional treatments⁶⁴. This hypothesis should be addressed in future studies to define the role of metronomic chemotherapy in advanced ACC.

Recently, Germano and colleagues presented the efficacy of gemcitabine alone or in combination with mitotane in ACC cell lines. Interestingly, in mitotane-sensitive cells the combination of these two drugs showed an antagonistic effect. Paradoxically, in mitotane-insensitive cells the same drug combination was synergistic, except when mitotane was sequentially administered prior gemcitabine. One explanation for these findings may be a different interaction with the Ribonucleotide Reductase large Subunit 1 (RRM1) gene. Further investigations are needed to define the role of gemcitabine in ACC treatment⁶⁵.

3.4.3. Molecular Pathways and Targeted Therapies—A better understanding of ACC biology has provided some rationale for the development of novel agents in this disease. Unfortunately, new agents have resulted and minimal or no activity and new investigations/clinical trials need to be encouraged to incorporate this strategy in the clinical practice. Here we summarize the existing evidence and potential pathways and targeted drugs that are being studied in ACC (Table 3).

3.4.3.1. Vascular Endothelial Growth Factor (VEGF) Pathway: Sunitinib is a small molecule tyrosine kinase inhibitor (TKI) involved in tumor proliferation and angiogenesis targeting platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor 2 (VEGFR2), stem cell factor receptor (c-KIT) and fms-related tyrosine kinase 3 (FLT-3) pathways⁶⁶. This drug produces important anti-tumor activity in different tumors and is widely used in renal cell carcinoma and gastrointestinal stromal tumor (GIST)⁶⁷. Interestingly, ACC is characterized by higher levels of VEGF expression than others adrenal tumors. In preclinical models sunitinib induced adrenal hemorrhage, leading to adrenal insufficiency^{68,69}, and down-regulated *HSD3B2* gene blocking steroidogenesis in vitro⁷⁰.

Based on these pre-clinical data, a phase II, single arm, trial was conducted to evaluate the efficacy of sunitinib in 35 patients with refractory ACC who had progressed after mitotane and 1 to 3 previous chemotherapies. The median PFS was 2.8 months and the response rate was 15.4%. More than half of the patients enrolled in this study received mitotane concomitantly. Notably, a drug interaction between sunitinib and mitotane might result in

reduced sunitinib levels by induction of cytochrome P450-3A4 activity. These findings may explain the modest antitumor activity of sunitinib reported in this study⁷¹.

Sorafenib is another multi-targeted TKI inhibitor targeting VEGF and angiogenesis. This agent was evaluated in a phase II trial in combination with weekly paclitaxel. Nine patients were enrolled. However this trial had to be stopped prematurely because all patients progressed after 8 weeks of treatment⁷².

Ten patients with advanced ACC who failed to prior cytotoxic agents were treated with bevacizumab and capecitabine combination on a compassionate use basis. None of these patients experienced any objective response or SD⁷³.

3.4.3.2. Epidermal Growth Factor Receptor (EGFR) pathway: Inhibition of EGFR pathway results in clinical benefit in several malignancies like non small cell lung cancer (NSCLC) and pancreatic cancer^{74,75}. Recently, Fassnatch and colleagues reported that 78% of ACCs express EGFR by immunohistochemistry, though none of the tumors harbored EGFR mutations in exons 19–21,⁷⁶. In a small study of patients with ACC progressing after two to four systemic therapies, salvage chemotherapy using gemcitabine plus erlotinib had no benefit among 10 patients who received this treatment⁷⁷.

A small North American phase II clinical trial addressed the efficacy of gefitinib in 19 patients. No complete responses, partial responses or patients with SD were also observed⁷⁸.

3.4.3.3. Insulin-like Growth Factor 1 Receptor (IGF-IR) Pathway: The IGF-IR is a transmembrane receptor with tyrosine kinase activity and is overexpressed in several malignancies. This seems to be the most common molecular event in ACC, but the molecular mechanism involved in this process is still unknown⁷⁹. Using DNA microarray Barlaskar and colleagues showed that the majority of ACC overexpressed *IGF* gene transcripts⁸. Two pathways are closely related to IGF-1R cascade: the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR and the RAS/MAPK pathways. The IGF-1R phosphorylation activates PI3K/AKT signaling pathway leading to cell survival. Similarly, it activates RAS and extracellular-signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway leading to tumor growth and proliferation⁸⁰.

Cixutumumab (IMC-A12) and figitutumumab (CP-751,871) are IGF-IR-targeting antibodies currently in development to block the interaction between IGF-IR and its ligand⁸¹. Figitutumumab was evaluated in a phase I study which enrolled 14 patients with advanced ACC. Eight of 14 patients (57%) had stable disease as their best response and none remains on therapy after 7 cycles due to progressive disease (PD) or toxicity⁸². Notably, 10 patients with ACC were treated with cixutumumab alone in a phase II study and no objective responses were reported. One patient achieved SD for 7 cycles⁸³. In addition, a small-molecule TKI of the IGF-IR (OSI-906) is being investigated. In a phase I study presented in the American Society of Clinical Oncology (ASCO) Annual Meeting in 2010, 1 patient with ACC had SD for more than 1 year. Results from this phase I trial led to the development of a randomized, placebo-controlled, phase III trial with this compound⁸⁴. Results from this study that finished accrual are awaited (GALACCTIC - NCT00924989).

3.4.3.4. Mammalian Target of Rapamycin (mTOR) Pathway: mTOR is a protein kinase of PI3K/AKT signaling pathway which regulates cell growth, metabolism, and proliferation⁸⁵. Pre-clinical studies have shown the anti-proliferative effect of the dual PI3K/mTOR inhibition in adrenocortical cell lines and xenograft models^{86,87}. These findings support the study of mTOR inhibitors in refractory ACC. Recently, a phase I study evaluated IMC-A12, a human IgG₁ monoclonal antibody to the IGF-1R, in combination with temsirolimus in patients with advanced cancer including 10 patients with ACC. In this study, 4 of 10 patients with ACC had SD as best response lasting 8 months. Among them, 2 patients presented tumor reduction without RECIST criteria of PR. PD was the best response in the other patients. Further investigations are needed to establish whether dual inhibition of the IGF-1R and mTOR pathways will impact in clinical outcomes of ACC patients⁸⁸. Interestingly, targeting this pathway with everolimus alone resulted in no meaningful responses⁸⁹.

3.4.3.5. Wnt/ β -catenin Pathway: β -catenin is important for the adrenal physiological maintenance and is a part of the Wnt signaling pathway which regulates the tissue self-renewal⁹⁰. Mutations in *APC* and *CTNNB1* genes, which encode this protein, have been described in several malignancies⁹¹. Interestingly, this pathway is also upregulated in ACC and may be a new target for therapeutic intervention⁹². The rationale to test this drug as a potential new therapy came from an experiment in which a β -catenin antagonist inhibited proliferation in ACC cell lines⁹³. Studies demonstrating the efficacy of this strategy in ACC treatment are not published up to the time this review was performed.

3.4.3.6. Other Targeted Agents and Approaches

3.4.3.6.1. Imatinib: Imatinib mesylate, is a small molecule selective inhibitor of the c-ABL, PDGFR and c-kit tyrosine kinases. Dramatic responses are seen in gastrointestinal stromal tumors (GIST) treated with Imatinib. Additionally, patients with other solid tumors expressing c-kit and/or PDGFR have also shown responses to this agent. A phase II trial evaluated the role of imatinib in a variety of solid tumors including 4 patients with ACC. No clinical benefit was reported in this subgroup of patients⁹⁴.

3.4.3.6.2. Dovitinib: Dovitinib is a multi-target TKI that inhibit the fibroblast growth factor receptor (FGFR). Pre-clinical studies have suggested that this pathway may play a role in ACC carcinogenesis. Recently, the first results from a phase II trial to evaluate the efficacy of this drug in 17 patients were presented. No objective response was observed. However, clinical benefit was achieved with SD for > 6 months in 23% of the patients⁹⁵.

3.4.3.6.3. Polo-like kinase 1 (PLK1) inhibitors: Polo-like kinase 1 (*PLK1*) gene is involved in multiple aspects of cell progression and is highly expressed in several malignancies. Agents against *PLK1* have been investigated in advanced solid tumors. Results from a phase I study to evaluate a small interfering RNA (siRNA) inhibiting *PLK1* were presented in the last ASCO annual meeting. This study included 4 patients with ACC in the expansion cohort. Among the ACC patients, 3 presented SD and the longest duration of response was 6 months. In addition, 1 patient had tumor size reduction of 19.3% after 2 cycles on therapy⁹⁶.

Further investigation is warranted to define the role of PLK1 inhibition in patients with advanced ACC.

3.4.3.7. Combination of Targeted Therapies: The combination of targeted therapies to block synergistically different pathways at the same time is being investigated in solid tumors to overcome therapy resistance. As mentioned before, combinations using mTOR inhibitors may be an important therapeutic option considering its impact in cell metabolism and pathways interactions⁸⁸. Moreover, single agent targeted therapies do not result in markedly responses.

A phase I study examined the safety and clinical effect of combination therapy targeting the VEGF pathway. In this study, bevacizumab plus sunitinib were evaluated in different advanced solid tumors, including 5 patients with ACC. This regimen showed some tumor activity across all tumor subtypes. 2 out of 5 patients with ACC presented some tumor reduction. However, higher toxicities levels were reported⁹⁷. Another phase I study of sorafenib and bevacizumab in patients with refractory, metastatic or unresectable solid tumors is ongoing and may help us to answer this question. (NCT00098592). A combination of anti-IGF-IR and EGFR-targeted therapy (OSI-906 + Erlotinib) is under investigation and in ACC. However, what is the optimal combination to treat ACC remains an important question.

4. Future Directions

Advanced ACC is a very aggressive disease and its management is challenging. During the past 10 years collaborative efforts have been made to improve the ACC treatment. Although multidisciplinary approaches may result in long-term disease control and survival, conventional chemotherapy is not curative and targeted therapies did not yield so far any noticeable results. The combination of mitotane plus EDP offer the best approach to extension of survival based on a rigorous and large study. However, effective treatments are lacking and these efforts have resulted in minimal progress in disease outcomes.

In the genomic era, the understanding of the ACC biology may lead to improvements in therapeutics. The Cancer Genome Atlas (TCGA) has allowed the molecular characterization of a large number of tumors, and an initiative for ACC is ongoing (Ref: <https://tcga-data.nci.nih.gov/tcga/tcgaCancerDetails.jsp?diseaseType=ACC&diseaseName=Adrenocorticalcarcinoma>). It may help us identifying new targets for therapeutic interventions and biomarkers that can predict response to targeted therapies. In addition, the role of immune regulation in tumor progression and metastasis has been investigated and the interest in this subject is tremendously increasing. As an example, blocking programmed death-1 (PD-1), an inhibitory receptor expressed on activated T cells, results in significant antitumor activity in several malignancies. Efforts should be also done to clarify the potential of novel immunotherapies to treat ACC and at least to interrogate the expression of the PD-1 ligand on tumor cells.

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Biography

André P. Fay is a medical oncologist. Since July 2013, Andre is working with clinical and translational research in the Lank Center of Genitourinary Oncology at Dana-Farber Cancer Institute/Harvard Medical School under Dr. Toni Choueiri's mentoring. Recently, He was selected to receive the MERIT Award of American Society of Clinical Oncology (GU ASCO Symposium 2014) with the research project: PD-L1 expression in non-clear cell renal cell carcinoma. Toni Choueiri is the clinical director and Kidney cancer Center director of the Lank Center of Genitourinary oncology and has contributions as a researcher, clinician and mentor of many oncology trainees. His research interests include the development of novel agents and biomarkers in genitourinary cancers, with a particular focus in renal cell carcinoma. Dr. Choueiri is currently the overall primary investigator in several phase I, II and III studies of novel agents and combinations using both clinical and correlative tissue-based endpoints.

Figure 1.
Flow Diagram

Table 1

Hereditary ACC-related Hereditary Syndromes

Hereditary Syndrome	Chromosome alterations	Gene	Comments
Li-Fraumeni Syndrome ¹⁰	17p13	<i>TP53</i> <i>hCHK2</i>	Mutations in TP53 are present in about 25% of sporadic ACC
Beckwith-Wiedemann Syndrome ¹⁰	11p15	<i>IGF-2</i> <i>CDKN1C</i> <i>H19</i>	Macroglossia, macrosomia, Wilms' tumour, ACC
Multiple Endocrine Neoplasia I (MEN I) ¹⁰	11q13	<i>MEN1</i>	Adrenal adenomas did not present alterations in this locus
Carney Syndrome ¹⁰	17q22-24	<i>PRKARIA</i>	53% of sporadic ACC
Lynch Syndrome (LS) ⁹	2p16 2q31 3p21 2p16	<i>MSH2</i> <i>PMS1</i> <i>MLH1</i> <i>MSH6</i>	The prevalence of LS among patients with ACC is 3.2%

Table 2

Cytotoxic Chemotherapy in ACC

Drug	Study Phase/n	Clinical Benefit
cisplatin + etoposide followed by mitotane ⁵⁹	II/n=47	ORR:11% Median OS: 10 months
M/EDP ⁶⁰	II/n=28	CR: 2 patients PR: 13 patients ORR 53.5%
SM ⁶¹	II/n=22	ORR: 36.4%
M/EDP vs. SM FIRMACT trial ⁶²	III/n=304	PFS: 5.0 vs 2.1 months(p<0.001) OS: 14 vs 12 months (p=0.07) ORR: 23.2 vs 9.2%, (p<0.001)

M/EDP: Mitotane + etoposide, doxorubicin, and cisplatin; SM: streptozotocin + mitotane

Table 3

Targeted Therapies in ACC

Drug	Target	Study Phase/n	Clinical Benefit
Sunitinib ⁷¹	VEGF pathway	II/n=35	5 patients with SD
Sorafenib + Paclitaxel ⁷²	VEGF pathway + Cytotoxic Chemotherapy	II/n=9	No Activity
Bevacizumab + Capecitabine ⁷³	VEGF pathway + Cytotoxic Chemotherapy	II/n=10	No activity
Erlotinib + Gemcitabine ⁷⁷	EGFR pathway	II/n=10	1 patient with SD
Gefitinib ⁷⁸	EGFR pathway + Cytotoxic Chemotherapy	II/n=19	No activity
Everolimus ⁸⁹	mTOR pathway	II/n=4	No activity
Imatinib ⁹⁴	C-ABL, PDGFR and C-kit Tyrosine kinase inhibitor	II/n=4	No activity
Cixutumumab (IMC-A12) ⁸⁴	IGF-IR pathway	II/n=10	1 patient with SD
Figitumumab ⁸²	IGF-IR pathway	I/n=14	8 patients with SD
Cixutumumab + Temsirolimus ⁸⁸	IGF-IR pathway + mTOR pathway	I/n=10	4 patients with SD

VEGF= vascular endothelial growth factor; EGFR= epidermal growth factor receptor; mTOR= mammalian target of rapamycin; IGF-IR= insulin growth factor 1 receptor; PDGFR= platelet-derived growth factor receptor;