Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2016 June ; 23(3): 233–241. doi:10.1097/MED.0000000000000247.

Novel Targeted Therapies in Adrenocortical Carcinoma

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Abstract

Purpose of review—Adrenocortical carcinoma is a rare cancer, but one that carries a poor prognosis due to its aggressive nature and unresponsiveness to conventional chemotherapeutic strategies. Over the past 12 years, there has been renewed interest in developing new therapies for this cancer, including identifying key signaling nodes responsible for cell proliferation.

Recent findings—Clinical trials of tyrosine kinase inhibitors as monotherapy have generally been disappointing, although the identification of exceptional responders may lead to the identification of targeted therapies that may produce responses in subsets of patients. Agents targeted to the Wnt signaling pathway, a known player in adrenal carcinogenesis, have been developed although have not yet been used specifically for adrenal cancer. There is current excitement about inhibitors of acetyl-coA cholesterol acetyl transferase 1 (ACAT1), an enzyme required for intracellular cholesterol handling, although trials are still underway. Tools to target other proteins such as SF1 and mTOR have been developed and are moving towards clinical application.

Summary—Progress is being made in the fight against adrenocortical carcinoma with the identification of new therapeutic targets and new means by which to attack them. Continued improvement in the prognosis for patients with adrenal cancer is expected as this research continues.

Keywords

Adrenocortical carcinoma; Receptor tyrosine kinase inhibitors; Wnt inhibitors; ACAT1 inhibitors; mitotane

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Conflicts of Interest

None

1. Introduction

Adrenocortical carcinoma (ACC) is a rare cancer but one in which there has been significant interest in the development of new therapeutics (1, 2). Although adrenal nodules are present in approximately 5% of the adult population, ACC remains rare, with an incidence between 0.5 and 2 cases per million worldwide (3) and 2.9–4.2 cases per million annually in Southern Brazilian children (1). The 10-fold increase in incidence in Southern Brazil is accounted for by the highly prevalent R337H germline mutation of the TP53 gene (1, 4). Although rare, ACC is aggressive, as it accounts for between 0.04 and 0.2 percent of all cancer deaths with a moderate female predominance. ACC appears to be most common in the 4th and 5th decades in life, although there is a second peak in early childhood, likely related to genetic predisposition syndromes such as Li-Fraumeni Syndrome and Beckwith-Wiedemann Syndrome. The disease in young children seems to behave differently compared with adults, as pediatric tumors are much more often androgen producing tumors and the prognosis is better. ACCs are most commonly staged by the criteria developed by the European Network for the Study of Adrenal Tumors (Table I). Under these criteria, about 35% of patients present with adrenal disease only (stage I and II), 18% with locally invasive disease (stage III), and 47% with metastatic disease (stage IV). The 5-year cancer specific mortality-free survival rates are approximately 74% (Stage I), 64% (Stage II), 44% (Stage III), and 7% (Stage IV) in the North American experience, indicating the pressing need for systemic therapies (5). Between 60 and 70% of adult ACCs are secretory tumors, and patients with secretory tumors tend to have a slightly worse prognosis. For a more thorough discussion of the general topic of ACC, readers are referred to a number of excellent recent reviews (1, 2).

2. Current therapies for ACC

Mitotane

Mitotane (1,1 dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane; o,p'-DDD) is an adrenolytic agent derived from the insecticide Dichloro-diphenyl-trichloroethane (DDT) (6). Its action on the adrenal cortex was described over 5 decades ago, when the drug was noted to cause degeneration of the zona reticularis and zona fasciculata while sparing the zona glomerulosa in dogs (7). Subsequent studies in humans uncovered the drug's potential to alter extra-adrenal metabolism of cortisol in addition to inhibiting steroid biosynthesis (8–10). Hydroxylation and dehydrochlorination of mitotane results in the formation of a reactive acyl chloride metabolite that either binds to adrenal macromolecules mediating mitotane's adrenolytic activity, or is metabolically transformed to o,p'-dichlorodiphenyl acetic acid (o,p'-DDA) (11). More recently, molecular studies on the pluripotent NCI-H295 cell line have shown that mitotane inhibits adrenocortical Sterol-O-Acyl Transferase 1 (SOAT1, also known as acetyl-coenzyme A:cholesterol O-acetyltransferase 1 *vide infra*) leading to accumulation of toxic lipids which in turn elicit endoplasmic reticulum stress and apoptosis in ACC (12).

Retrospective studies have suggested that mitotane has a narrow therapeutic window with sustained maintenance of a serum level 14 mg/L predicting a better recurrence-free survival (RFS) in the adjuvant setting (13), while improving tumor response and survival in advanced

ACC (14, 15). Adverse effects include nausea, vomiting, diarrhea, and neurological effects such as lethargy, dizziness, cerebellar ataxia and neuropsychiatric effects (14, 16), with levels >20 mg/L associated with grade 3 or 4 neurologic toxicity (15). In addition, other factors such as CYP2W1 (17) and SOAT1 expression (12) influence the drug's efficacy in ACC. Despite these problems, mitotane is currently the only drug that carries the specific indication for ACC therapy from the United States Federal Drug Administration (FDA).

Mitotane as adjuvant therapy—A mere 30% disease-free survival (DFS) despite radical surgery in patients with ACC calls for effective adjuvant therapy (18). Several retrospective studies have supported the use of mitotane after complete surgical resection in these patients (Table 2). Interestingly, in a recent large multicenter retrospective analysis of 207 patients, adjuvant mitotane was not associated with RFS or OS on multivariable analysis (Table 2). Of note however, only 32/88 (36%) patients who received mitotane in this study had serum mitotane levels available, of which only 15 patients had levels between 14–20 mg/L. Thus, no definitive conclusions can be drawn from this study (19). With similar controversial results noted in small prospective studies (20, 21), there is an urgent need for large randomized prospective trials evaluating the efficacy of mitotane in the adjuvant setting. ADIUVO (NCT00777244) is one such study; the results of which are awaited (22).

Mitotane in advanced ACC—The paucity of well-designed clinical trials makes the role of mitotane monotherapy in the metastatic setting speculative at best. In a single center prospective study by Baudin et al, of the 13 patients with metastatic disease who received mitotane therapy, only 4 (31%) had an objective tumor response (15). Paradoxically, in a retrospective series of 115 patients with inoperable ACC treated with mitotane, an impressive 61% (46 of 75 evaluable patients) and 54% (54 of 100 evaluable patients) had measurable disease response and overall clinical response respectively. The median duration of treatment was 4 months, with a median time to tumor response of 4 weeks (16). However, the retrospective nature of this study prevents us from drawing definitive conclusions.

Cytotoxic chemotherapy

Select studies evaluating the role of cytotoxic chemotherapy in advanced ACC are summarized in Table 3. While most of the chemotherapy combinations failed to evoke enthusiasm, reasonable objective responses of 53.5% (27) and 34.8% (20) were noted with the use of Etoposide/Doxorubicin/Cisplatin/Mitotane (EDP-M) and Streptozocin/Mitotane (Sz-M) respectively. The First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) evaluated the efficacy of first-line EDP-M versus Sz-M in these patients. The EDP-M arm had significantly higher objective responses and progression-free survival (PFS) when compared to the Sz-M arm, in addition to a 21% reduction in the risk of death in the former arm in the intent-to-treat analysis. Given the high probability of treatment failure with first line therapy, patients were allowed to cross-over to the alternative chemotherapy regimen on progression or in the event of intolerable adverse effects. The study design thus incorporated 2 additional phase II trials evaluating second-line therapy in these patients. A total of 185 patients (61%) went on to receive second-line therapy, with median PFS (5.6 v 2.2 mo) and median duration of survival

(10.3 v 7.4 mo) with second-line therapy again favoring the EDP-M arm (28). EDP-M has thus become the standard first-line chemotherapy option in patients with advanced ACC.

Metronomic chemotherapy refers to the administration of small but frequent doses of uninterrupted chemotherapy over extended periods of time, in doses much less than the maximum tolerated dose (MTD) (33). In contrast to traditional chemotherapy, which primarily targets rapidly proliferating cells, metronomic therapy inhibits tumor angiogenesis, hence aptly referred to as anti-angiogenic chemotherapy (34). This novel strategy also has an immunomodulatory role, and can improve drug efficacy and tolerability, while overcoming drug resistance (35). In a phase II trial of 28 previously heavily treated patients with advanced ACC, 46.4% had no progression after 4 months of therapy with metronomic 5-Fluorouracil (5FU) /capecitabine and gemcitabine. However, with only a 7.1% objective response rate and a 9.8 month OS, these results call for guarded optimism at best (32).

Temozolamide is an oral alkylating agent (36) that deserves mention, though not extensively explored in ACC. Early in vitro data suggests potential activity against human primary adrenal carcinoma colony forming units with a 33% (1/3 specimens) response rate at a temozolamide concentration of 10 μ M (37). More recently, studies on human ACC cell lines have shown temozolamide to have apoptotic (38, 39) and cytotoxic effects, particularly at concentrations of 25 μ M, with activity noted despite expression of O6-Methylguanine-DNA methyltransferase (MGMT) (40). As expected, sensitivity of temozolamide was inversely proportional to MGMT expression (38). Future in vivo studies are needed to corroborate these findings.

3. Targeted therapies – Receptor Tyrosine Kinases

Targeting the angiogenic receptor tyrosine kinases

Vascular endothelial growth factor (VEGF), VEGF Receptor 2 (VEGFR2), and heparanase-1 (HPA-1) mediate tumor angiogenesis and proliferation, and show increased expression in ACC (41, 42). It would therefore only be intuitive to assume that anti-angiogenic agents would have a promising role in the treatment of ACC. Unfortunately, clinical studies have proven otherwise.

Bevacizumab is a monoclonal antibody that binds to VEGF thereby blocking its interaction with VEGF receptors (43). Taking advantage of the anti-angiogenic properties of metronomic therapy, the combination of metronomic capecitabine and bevacizumab was studied in 10 patients with unresectable/locally advanced/metastatic/recurrent ACC who had progression on prior mitotane and at least 2 lines of chemotherapy including EDP and Sz. Contrary to expectations, the study yielded disappointing results with no objective responses or stable disease (SD) noted (44).

Sorafenib is a multiple receptor tyrosine kinase inhibitor (TKI) that inhibits VEGFR2-3, platelet-derived growth factor (PDGFR), and the enzyme RAF-1. Its role in combination with metronomic paclitaxel was studied in a multicenter phase II study that enrolled 25 patients with metastatic ACC who had progressed on mitotane and at least 1 prior cisplatin-

based chemotherapy regimen. The trial was prematurely interrupted after all evaluable patients (9/9) had disease progression on their first 8 week evaluation (45).

Sunitinib is a multi-TKI that inhibits VEGFR1-2, c-KIT, Fms-like tyrosine kinase 3, and PDGFR. In a prospective open label phase II study of 35 evaluable patients with advanced ACC, only 5 patients (14.3%) had SD, while the rest either had progressive disease (24/35) or died (6/35) prior to first assessment. Median PFS was a meager 2.8 months with a median OS of 5.4 months. However, with mitotane being an inducer of cytochrome P450-3A4, its concomitant use in these patients could have affected the study results by lowering serum levels of sunitinib and its active metabolite (46). A future study evaluating the efficacy of sunitinib in patients not on mitotane, or monitoring sunitinib levels in patients on concomitant sunitinib and mitotane is called for.

Axitinib is a small molecule TKI that targets VEGFR1-3. Its role in ACC was evaluated in an open label, phase II trial of 13 previously treated patients, all of whom had metastatic disease. There were no objective responses, and SD for over 3 months was noted in 8 patients. The median PFS of 5.48 months, and OS of 26.92 months were relatively overly optimistic and thought to be secondary to the inherent indolent nature of the tumor in these patients who had a median OS of nearly 3 years prior to trial enrollment (47).

Targeting the epithelial growth factor receptor (EGFR)

Several studies have shown that the majority of ACC tumor samples express EGFR (48–50) which is known to regulate cellular proliferation (51). This finding led to interest in evaluating the role of EGFR TKI in patients with advanced ACC (52, 53)

Erlotinib is a EGFR TKI (54) that was studied in combination with gemcitabine in a series of 10 patients with metastatic/recurrent/unresectable/locally advanced ACC who had progression on mitotane and at least 2 chemotherapy regimens, including a platinum-based regimen. Results were dismal with only 1 patient having a minor response to therapy with a PFS of 8 months. 9/10 patients had a median survival of 5.5 months after initiation of therapy (52).

Gefitinib is another EGFR TKI that has been studied in a phase II trial to evaluate its role in the second-line setting in patients with unresectable ACC who had progressed on prior mitotane or chemotherapy. Unfortunately, of the 19 evaluable patients, none had an objective response or SD (53). Thus, EGFR TKIs cannot be recommended as a treatment option in patients with advanced ACC.

Targeting the Insulin-like Growth Factor 1 Receptor (IGF1R)

Human IGF1 and 2 are cell growth regulatory and mitogenic polypeptides that are structurally similar to human insulin (55) and exert their effects via the type I IGF receptor (IGF-1R) (55–57). 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 (57). In addition to IGF-1R which serves as a receptor for IGF1 and 2, Insulin Receptor-A (IR-A) binds IGF2 with increased affinity and thus plays a pivotal role in cell growth and differentiation (58).

IGF1, IGF2, and IGF-1R are expressed by normal human adrenocortical cells with significant overexpression of IGF2 (59) and IGF-1R in ACC(60). In addition, IR has also been shown to have increased expression in several solid tumors (61). It was therefore hypothesized that IGF1R and IR could be potential therapeutic targets in clinical studies.

Lensitinib (OSI-906), a dual inhibitor of both IGF-1R and IR, was studied in humans for the first time in an open-label, phase I study of 79 patients with advanced solid tumors, of which 15 patients had ACC. The MTD was 600 mg/day, and though efficacy was not the primary end point of the study, 2 patients with ACC had partial responses (61). Encouraged by these results, Lensitinib versus placebo was studied in a double-blind placebo controlled phase III trial of 139 patients with locally advanced or metastatic ACC who progressed on at least one but no more than three prior lines of therapy, having had received mitotane either in the neoadjuvant/ adjuvant/ advanced disease setting. Unfortunately, Lensitinib failed to show a difference in median OS (323 v 356 days, p 0.77) or PFS (44 v 46 days, p 0.30) when compared to placebo (62).

Cixutumumab (IMC-A12) is a recombinant human monoclonal IGG1 antibody against IGF-1R. Its combination with mitotane as first-line systemic therapy was studied in a multicenter phase I run-in single arm study of 20 patients with unresectable or metastatic ACC, with plans for a subsequent phase II randomized trial comparing the efficacy of cixutumumab plus mitotane with mitotane alone. The drug combination had no clinically meaningful outcome, with only 1 PR and 7 patients with stable disease. The median PFS was 6 weeks. The study was therefore prematurely terminated soon after the initial run-in phase (63).

Targeting mTOR

The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase and member of the PI3 kinase/AKT family, that mediates cell growth and proliferation (64). The combination of an mTOR inhibitor (Temozolimus), and an immunomodulatory agent (Lenalidomide), was evaluated in a phase I study of 43 patients with advanced cancers, including 3 patients with ACC. 1/3 (33%) patients with ACC had SD for at least 6 months in this study (65). Temozolimus was also studied in combination with Cixutumumab in a phase I dose escalation study of 42 patients with advanced cancers who had received a median of 4 prior therapies. Of the 10 patients with advanced ACC in the study, 4 (40%) had stable disease for over 8 months (66). In the subsequent dose expansion cohort, 11/26 (42%) patients with advanced ACC had SD for at least 6 months, despite 3 of these patients having previously received IGF-1R inhibitor therapy (67). These encouraging data warrant future larger studies with this drug combination.

Other RTKs

Analysis of mRNA expression patterns (68–73) and mutation patterns (74) in ACC has also revealed potential targets for ACC therapy, including the FGF receptor and c-MET (75). An ongoing phase 1/2 study (NCT01752920) of the pan-FGFR inhibitor ARQ087 included one patient with ACC who had disease stabilization lasting for an extended period (76). Similarly, a phase I trial of a Met inhibitor included a single patient with ACC who appeared

to derive some benefit (77). As of yet, these kinases have not been targeted in trials directed towards ACC.

Targeted therapies – Other potential targets

Wnt—The Wnt/ β -catenin signaling pathway is an important developmental pathway in many organs, including the adrenal gland. Analysis of tumors has demonstrated that mutations in β -catenin (encoded by *CTNNB1*) are seen in cancers (78, 79), and expression analyses have confirmed a Wnt/ β -catenin expression pattern, generally associated with more aggressive tumor behavior (68, 80).

Because Wnt/ β -catenin signaling has been implicated in multiple tumor types (most notably colon cancer), there has been significant interest in developing compounds which inhibit this pathway. One approach to drugging the Wnt pathway has been the development of inhibitors of the PORCN (Porcupine), a membrane protein required for secretion of Wnt ligands (81, 82). Two compounds in this class (LGK974 and ETC-1922159) are currently in early phase clinical trials, although no results have been reported. A chimeric antibody which competes for extracellular Wnt ligands has also been developed (83). It has done well in a phase I study (84) and is currently being tested in combination therapies for specific non-adrenal cancers.

Because β -catenin can be activated directly by mutations, agents that target the pathway at the post-receptor level may be necessary for efficacy. CWP232291 is a drug that appears to suppress Wnt signaling by promoting β -catenin degradation (85), and this agent is currently in early phase I trials for leukemia (86). PRI724 is another agent which targets this pathway, in this case by blocking the interaction of β -catenin with transcriptional partners. Phase I studies have showed acceptable toxicity, and studies of this drug in isolation or in combination are ongoing (87, 88). It is important to note however that 27% of benign adrenocortical tumors harbor β -catenin mutations (89); therefore, whether this is a targetable therapy for adrenal malignancies is challenging to decipher.

SF1—SF1 is a transcription factor that is essential in adrenal development. In recent years, amplification and overproduction of this protein have also been implicated in ACC (90). Because of the relationship between this protein and adrenal function, efforts have been undertaken to develop compounds that affect the transcriptional activity of SF1 (91, 92). Although inverse agonists of SF1 have been demonstrated to be successful at reducing the proliferation of ACC cell lines (92), this line of study has not yet engendered clinical trials.

ACAT1—Acetyl-coenzyme A:cholesterol O-acetyltransferase 1 (ACAT1) is an enzyme that has recently gained some interest as a potential target for therapy for ACC (93). It is an enzyme typically located in the endoplasmic reticulum (ER), where it catalyzes the esterification of intracellular free cholesterol into cholesterol esters. Inhibitors of the enzyme were initially developed as potential therapeutics for cardiovascular disease targeted towards reducing building of cholesterol esters in macrophages (94). However, studies in animals revealed the presence of adrenal toxicity (95), leading to its consideration for use in adrenal tumors (93). Although no results from the trial are yet available, mechanistic studies have suggested that inhibition of ACAT1 in the presence of cholesterol causes ER stress and

calcium release in adrenocortical cells, leading to cell death (96). These studies have also suggested that this same mechanism may be responsible for mitotane-induced adrenocortical toxicity.

Immunotherapy—Immune check point inhibitors have shown promising results in various malignancies (97, 98), however their role in ACC is yet to be explored. A step in this direction was a small exploratory study evaluating the expression of PDL1 in ACC tumor specimens and identifying its clinicopathological correlates. Though PDL1 was noted to be expressed in ACC cells and tumor infiltrating mononuclear cells (TIMC), there was no association between stage at diagnosis, tumor grade, tumor functionality, or OS (98). An ongoing prospective case-control phase 0 study (NCT00457587) is investigating the role of immunotherapy in ACC (99).

4. Conclusions and Future Direction

Despite the fact that ACC is a rare cancer, there has been significant interest in improving treatments for those patients whose disease cannot be surgically removed. This work has been spearheaded by an international network of scientists and clinicians whose work has been ongoing since the collaboration was initiated in 2003 (100). Although clinical progress has been slow, our understanding of the molecular basis of this aggressive cancer has continued to improve. In parallel, the toolbox for targeting specific signaling pathways (including those that were previously considered “undruggable”) has also continued to expand. Although progress may be slow, it is expected to continue so that future generations of physicians may be able to provide control and extended lifetimes to patients who have what is now a deadly disease.

Acknowledgments

The authors wish to thank Dr. Manisha Shah for her gracious help caring for these challenging patients.

Financial Support and sponsorship

This work was supported, in part, by grant CA016058 to the Ohio State University Comprehensive Cancer Center (LSK)

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Key Points

- Tyrosine Kinase inhibitors have largely been ineffective as monotherapy
- The Wnt signaling pathway remains a viable target, and tools to target this pathway are now coming online
- Inhibition of ACAT1 (acetyl-coA cholesterol acetyl transferase 1) is a promising new avenue of research
- Further research is needed for the identification of additional targets and the means to block them

Table 1

ENSAT staging criteria for ACC (1)

Stage	Characteristics
I	Tumor < 5 cm with no local invasion or metastasis
II	Tumor > 5 cm with no local invasion or metastasis
III	Any tumor size, with invasion into periadrenal fat, other local organs, or local lymph nodes
IV	Any tumor size, with distant metastasis

Table 2

Retrospective studies on adjuvant mitotane therapy

Study	Sam- ple size	Adjuvant mitotane	No adjuvant mitotane	Follow- up (media- n; mo)	RFS (median; mo)	p value signifi- cant (Y/N)	OS (median; mo)	p value signifi- cant (Y/N)
Terzolo et al (23)	177	47 [^]	55 [*] 75 [#]	56.7 [^] 67.6 [*] 43 [#]	42 v 10 [*] 42 v 25 [#]	Y Y	110 v 52 110 v 67	Y N
Berruti et al (24)	524	251	273	50	NR	Y	NR	N
Bertherat et al (25)	166	86	80	NR	NR	N ^{**}	NR	NR
Beuschein et al (26)	319	84	235	43.7	NR	N	NR	Y ^{^^}
Postlewait et al (19)	207	88	119	44	10 v 27.9 [‡] NR [∞]	Y [‡] N [∞]	31.7 v 58.9 [‡] NR [∞]	Y [‡] N [∞]

[^] cases, Italian;^{*} control group 1, Italian;[#] control group 2, German;^{**} noted only in multivariate analysis of 63 patients;^{^^} noted in multivariate analysis; NR= not reported;[‡] univariate analysis;[∞] multivariate analysis

Cytotoxic chemotherapy in advanced ACC

Table 3

Study	Regimen	Number of Evaluable patients	Objective response (%)	Response duration (median, mo)	Median survival (mo)
Bukowski (29) Phase II	Cisplatin/Mitotane	37	30	7.9	11.8
Berruti (27) Phase II	EDP-M	28	53.5	24.4 (TTP in responding pts)	NR
Khan (20) Phase II	Sz-M	23 [*]	34.8	NR	16 ^{**}
Williamson Phase II(30)	Cisplatin/VP16-> Mitotane at disease progression	45	11	NR	10
Abraham (31) Phase II	Doxorubicin/VP16/Vincris tine/Mitotane	35	22 [†]	12.4 (mean)	13.5
Sperone (32) Phase II	Gemcitabine/metronomic 5FU or Cape	28	7.1	5.3 (TTP)	9.8
Fassnacht (28) Phase III	EDP-M v Sz-M	304 151 (EDP- M) 153 (Sz- M)	23.2 v 9.2 (p<0.001)	5 v 2.1(PFS) (p<0.001)	14.8 v 12 (p 0.07)

^{*} 11 patients underwent radical surgery and received Sz-M on recurrence or when they developed metastatic disease, 12 patients had recurrent/metastatic disease at diagnosis;

^{**} in patients with advanced disease at diagnosis;

[†] includes minor responses; TTP=time to progression; mo=months