Management of adrenocortical carcinoma: are we making progress?

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***Abstract*:** Adrenocortical carcinoma (ACC) is a rare malignancy characterized by aggressive biology and potential endocrine activity. Surgery can offer cure for localized disease but more than half of patients relapse and primary unresectable or metastasized disease is frequent. Prognosis of metastatic ACC is still limited, with less than 15% of patients alive at 5 years. Recent advances in understanding the molecular profile of ACC underline the high complexity of this disease, which is characterized by limited drugable molecular targets as well as by a complex interplay between a yet scarcely understood microenvironment and potential endocrine activity. Particularly steroid-excess further complicates therapeutic concepts such as immunotherapy, which have markedly improved outcome in other disease entities. To date, mitotane remains the only approved drug for adjuvant and palliative care in ACC. Standard chemotherapy-based protocols with cisplatin, doxorubicin and etoposide offer only marginal improvement in long-term outcome and the number of clinical trials conducted is low due to the rarity of the disease. In the current review, we summarize principles of oncological management for ACC from localized to advanced disease and discuss novel therapeutic strategies, including targeted therapies such as tyrosine kinase inhibitors and antibodies, immunotherapy with a focus on checkpoint inhibitors, individualized treatment concepts based on molecular characterization by next generation sequencing methods, the role of theranostics and evolvement of adjuvant therapy.

Keywords: adrenocortical cancer, chemotherapy, immunotherapy, tyrosine kinase inhibitors

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Introduction

With an incidence of 0.5–2 cases per million per year, adrenocortical carcinoma (ACC) represents a rare malignancy originating from the endocrine system.[1] Due to its localization, aggressive biology and ability to present with hormone-excess syndromes, ACC requires an early multidisciplinary approach usually involving endocrine surgeons, endocrinologists and medical oncologists. The only curative treatment is surgery for resectable tumors but despite a trend towards more patients being diagnosed with localized disease in recent years, up to two-thirds already present with metastatic disease frequently involving liver, lung and bone.[1–5] The prognosis of these patients is dismal with an estimated 5-year overall survival (OS) <15%. Standard chemotherapy-based treatment has not evolved over the last decade and offers only limited palliation with an unsatisfactory overall outcome. In the current review, we provide an overview on oncological care from limited stage to advanced ACC. In this article, we want to focus on recent developments and potential future systemic therapeutic strategies, including tyrosine kinase inhibitors, immunotherapy, theranostics and personalized therapy based on next generation sequencing (NGS) approaches.

Clinicopathological features of ACC

Clinical presentation

ACC is diagnosed more frequently in women than in men (ratio 1.5:1) and while the peak

incidence is reported around the fourth to fifth decade, ACC may occur at any age.[6] The initial diagnosis is often incidental, and every adrenal tumor detected upon imaging should be subject to structured hormonal and radiological assessment [computed tomography (CT) or magnetic resonance imaging (MRI) with specific adrenal protocols to define lipid content, size and washout].[1,7] The risk for an adrenal tumor to be ACC correlates with morphological presentation and size, and current guidelines recommend to consider surgical resection in adrenal tumors with malignant radiological features and/or a size of >4–6 cm. Surgery should also be considered in the case of tumor growth of greater than 5 mm in 6–12 months in lesions with atypical characteristics.[7] Preoperative biopsy (which requires definitive exclusion of pheochromocytoma) is advised only in the case of medical history suggesting secondary spread from another primary, as there is a substantial risk of tumor cell seeding with only poor diagnostic yield in a high percentage.[1] The majority of cases are considered sporadic but hereditary syndromes including Li-Fraumeni, multiple endocrine neoplasia (MEN) 1, congenital adrenal hyperplasia or the Beckwith–Wiedemann syndrome may be associated with ACC. A total of 60% of patients display endocrine activity, which is associated with an inferior prognosis.[3] Cushing's syndrome is the most common hormone-excess, while overproduction of the sexual hormone axis or hyperaldosteronism are less frequent.

From pathology to molecular targeted treatment

The pathological diagnosis of ACC remains challenging; typical differential diagnoses include cortical adenoma, pheochromocytoma, metastases (e.g. kidney, lung, liver, bladder, colorectal, melanoma) and sarcomas. Regarding cortical adenoma and ACC, there are still no satisfying clear-cut criteria for solid differentiation between the different entities of adrenal masses.[8] Basic immunohistochemical stainings include melan A, inhibin, calretinin and synaptophysin and allow for differentiation between cortical and medullary lesions.[8,9] In addition, immunohistochemical markers for differential diagnosis of adrenal metastases, including cytokeratins, and markers specific for steroid-producing cells, can be assessed. Steroidogenic factor 1 (SF-1), expressed ubiquitously by adrenocortical cells, has been defined as a powerful marker for diagnostic and prognostic purposes, as it is correlated with inferior outcome.[10,11] As immunohistochemical results can be variable in cases of ACC, a panel approach is recommended. So far, differentiation between adenoma and carcinoma is mainly based on various composed risk scores, including traditional conventional histomorphologic scores, invented by Hough *et al.*,[12] van Slooten *et al.*[13] and Weiss *et al.*,[14] with the Weiss score being the most commonly applied. The Weiss score was first presented in the late 1980s and includes nine easily identifiable pathological criteria, that is, nuclear grade, number of mitoses, presence of atypical mitoses, percentage of clear cells, diffuse architecture, confluent necrosis, and capsular, venous and/or sinusoidal invasion, which have not been essentially changed despite evolvement of novel technologies and molecular markers.[14,15] Aubert modified the classical Weiss score in 2002, reducing the original nine factors to five (number of mitoses, presence of atypical mitoses, percentage of clear cells, necrosis and capsular invasion).[16] For categorization of oncocytic ACC and oncocytic adenomas, the Lin–Weiss–Bisceglia criteria were introduced in 2004.[17] The Wieneke classification should be applied to pediatric ACC, as the Weiss classification cannot be used in these tumors.[18] For adult ACC the original Weiss score has been used by most pathologists, though some discussion is ongoing about its universal application. However, combining the Weiss score with some of the aforementioned scoring systems can be useful for borderline tumors, as some cases can pose a major diagnostic challenge. A defined cut-off for ACC is a Weiss score ⩾3 and the prognostic significance of this cut-off was confirmed in larger ACC series including also investigation of novel markers such as *MDM2* overexpression, a known negative regulator of *TP53*.[19] Despite recent efforts to streamline assessments, a high inter-observer variability has been reported and histological (re)assessment by a reference pathologist is recommended.[11,20] Another score more recently developed is the European Helsinki Score, focusing on mitotic count, Ki67 and presence of necrosis, which allowed prediction of the metastatic potential of ACC.[21,22] In general, there is increasing value of Ki67% assessment for measurement of proliferation; guidelines present strict cut-offs for guiding adjuvant therapy based on studies underlining the high prognostic impact of the Ki67-index following complete surgical resection.[1] For example, outcome differed significantly for a Ki67 <10% *versus* 10–19% *versus* ⩾20% in 319 patients with complete resection from the

German ACC registry (relapse-free survival 53.2 months *versus* 31.6 months *versus* 9.4 months, $p < 0.001$).[23]

For a deeper understanding of pathogenesis, molecular characterization of ACC to allow future development of novel therapies is of increasing interest. Somatic mutations resulting in loss of *TP53* and/or overexpression of the insulin-like growth factor II (*IGF-2*), with the latter being caused by (epi)genetic changes in the imprinted region of the gene at 11p15, are the most commonly reported alterations detected in up to 90% of patients.[24] In line with other tumor entities, *TP53* mutations are associated with worse prognosis.[25] Furthermore, activation of the β-catenin pathway and less frequently *EGFR*, *BRAF* and oncogenic *RAS* mutations are involved in tumorigenesis and might be of potential therapeutic interest.[11,24,26] Integrated genomic characterization series using exome sequencing and single nucleotide polymorphism (SNP) arrays confirm frequent driver genes to be *CTNNB1*, *TP53*, *CDKN2A*, *RB1* and *MEN1*.[27] A further extensive molecular profiling on 90 patients including exome sequencing, SNP arrays, DNA methylation profiling and reverse phase protein arrays has suggested also *PRKAR1A*, *RPL22*, *TERF2*, *CCNE1* and *NF1* as potential driver genes for ACC.[28] The authors have also discussed the impact of whole genome doubling on aggressiveness of ACC and defined three distinct clinical and molecular subtypes. However, it has to be clearly stated that so far no hallmark mutation has been detected for localized or advanced ACC,[24] and the impact of standard NGS panels for assessment of somatic mutations is not yet of routine therapeutic relevance, as discussed below.

Surgical management of ACC

Surgery is the only potentially curative therapy for patients with ACC and all patients with adrenal tumors suspect of malignancy. Therefore, patients without evidence of distant metastases and with tumors judged resectable should be offered surgery.[1,29] For planning of surgery, tumor extension should be assessed by MRI of the abdomen, while distant metastases can be excluded by CT scan of the thorax or (18)F-fluoro-2-deoxy-d-glucose positron emission tomography/CT (if available) and bone scintigraphy (in selected cases). As brain involvement is exceedingly rare at diagnosis, no dedicated imaging of the brain is routinely recommended in such patients.[30] Parallel to imaging, a biochemical work-up has to be performed, including assessment of a 1-mg dexamethasone-suppression test, plasma or urine metanephrines, sexual hormones and steroid precursors. In hypertensive and/or hypokalemic patients, evaluation of the aldosterone/renin ratio is mandatory.[7,29] There is a strong consensus that ACC patients should be treated in centers with more than 10 adrenalectomies per year and a high expertise in surgical visceral oncology.[29] In the case of ACC, it is of utmost importance not to injure the capsule of the tumor to avoid local spreading.[7,29] Thus, open surgery is preferable to minimal invasive methods in these patients. In the rare cases of ACC being smaller than 6 cm and/or in lesions with no pre-operative suspicion of ACC, minimal invasive methods will be chosen by most surgeons. If the tumor does not infiltrate other structures, surgery can be completed as planned if it is possible to keep the capsule of the tumor intact. With this approach, equal results to open surgery can be achieved.[31,32] In a recent review on the (dis)advantages of minimally invasive surgery for lesions susceptive for ACC,[33] lower intra-operative blood loss and shorter hospitalization durations were suggested for minimally invasive surgery, while open surgery was uniformly recommended as standard of care for stage III and IV ACC. In their analysis of reports, the authors nevertheless also conclude that open surgery still should be the method of choice also for localized stages in the case of suspected ACC. In the case of preoperatively proven extra-adrenal tumor spread without distant metastases and where resection is still feasible, an open en-bloc resection is recommended.[7,29] Local involvement of the liver may require wedge resections for R0-surgery and in the case of a tumor thrombus in the vena cava, a venovenous bypass or a cardiopulmonary bypass can be necessary to remove the thrombus. If a radical resection is not feasible, palliative surgery may be considered in patients with functional tumors. In the case of recurrent disease and low tumor burden, surgery can be effective in improving survival if an R0 resection is achievable and the time to first recurrence was >12 months.[6]

Adjuvant therapy of ACC

Up to 50% of patients undergoing curative surgery for ACC relapse, and a high number of cases present with distant metastases at first progression, which underlines the (yet unmet) need for effective adjuvant strategies.[1,34] The only approved

drug for the systemic treatment of ACC in both adjuvant and palliative setting is mitotane, a selective inhibitor of steroidogenesis that also displays direct cytostatic and (adreno)lytic effects to normal adrenocortical cells.[34] Current clinical practice guidelines provide specific recommendations for adjuvant mitotane treatment. In Europe, the European Society for Endocrinology (ESE) and European Network for the Study of Adrenal Tumors guideline, which is endorsed by the recently published European Society for Medical Oncology guideline, suggest mitotane for patients presenting with at least one risk factor of (1) stage III disease, (2) R1-Rx resection and (3) Ki67 > 10%.[1,2] In patients without these features, adjuvant therapy should be evaluated on an individual basis. While these recommendations appear straightforward, the underlying data are controversial. In detail, two meta-analyses and several retrospective series have suggested a reduced relapse risk +/− OS benefit for adjuvant mitotane but all these data are of retrospective nature.[1,2,35] A meta-analysis published by Tang *et al.*[35] included a total of five trials comprising 1249 patients. This analysis showed a prolonged relapse-free survival (RFS) with a hazard ratio (HR) of 0.62 [95% confidence interval (CI) 0.42–0.94, $p < 0.05$] and a significant increase in OS (HR 0.69, 95% CI 0.55–0.88, $p < 0.05$) for the overall population. A comparable study published within the ESE guideline reported a pooled HR for OS of 0.7 (95% CI 0.5–0.9).[7] Not yet included in these series is a recent Italian study (152 patients, 66% received mitotane) that suggested more narrow criteria and highlighted an OS benefit for Ki67 > 10% ($p = 0.005$) and stage III disease ($p = 0.02$).[36] In contrast to these results, in a US analysis of 207 patients and 13 centers, mitotane did not result in benefit for RFS/OS.[37] However, there was a high number of patients with stage IV, with a substantial percentage of patients being given mitotane along with chemotherapy, and while in fact an adverse trend was shown with inferior RFS for the mitotane group, OS appeared partly positively influenced. The current National Comprehensive Cancer Network (NCCN) guidelines provide a less apodictic recommendation for adjuvant mitotane compared with the European ones, without strict criteria regarding stage and Ki67 but only suggesting evaluation for mitotane in patients with a high risk for recurrence, such as a ruptured capsule, large size or high-grade histology.[38] The NCCN guidelines also clearly state that the evidence level for this recommendation remains low. However, recently an analysis of the National Cancer Database reported that survival of US patients receiving adjuvant therapy has improved since 2007 (5-year OS 41% *versus* 25%, $p = 0.02$).[4]

The only way to really make progress regarding the question of adjuvant mitotane in the near future will be to learn from clinical trials, such as the ADIUVO study (NCT00777244). In ADIUVO, a randomized phase III, patients with fully resected ACC are randomized to observation *versus* mitotane and results have been referred forward to basically every meeting in the last decade discussing this issue. However, ADIUVO-included patients do only partly meet the current recommendation criteria as only patients with a Ki67 < 10% are randomized. According to *ClinicalTrials.gov* the study had reached primary completion at the end of 2018 and results are being awaited.

While the European guidelines are valuable recommendations for our routine clinical approach, the lack of prospective data and the impact of mitotane treatment on the patient's quality of life, including potentially life-threatening complications caused by adrenocortical hormone-deprivation, are caveats that should be kept in mind. In view of this, the decision about adjuvant therapy should be made on an individual patient basis and following highly informed consent. The ADIUVO trial also collected patient reported outcomes, which will be of interest in this context. If mitotane is used for adjuvant therapy, drug levels need to be monitored closely as patients with mitotane levels >14 mg/L were more likely to have a prolonged benefit in RFS (HR 0.418, 0.22–0.79, $p = 0.007$).[39] In addition, a recent publication underlined that mitotane concentrations are strongly affected by gender as female patients treated with adjuvant mitotane showed significantly lower levels (7.6 mg/L *versus* 11.0 mg/L, $p = 0.007$) but were also more likely to experience toxic concentrations (8% *versus* 5%), which should be considered in the dosing process.[40] As current recommendations for adjuvant therapy are not fully satisfactory, assessment of potential biomarkers is of interest. The epithelial–mesenchymal transition related genes *FSCN1* and *FOXM1* were both strong independent negative prognostic factors if overexpressed in localized or advanced ACC and were suggested to be used as predictive tools.[41,42] However, there is no current consensus on the relevance of molecular markers in ACC. Prospective trials, ideally of randomized

nature, are clearly warranted, as little progress in tailoring adjuvant treatment has been achieved in the last decade.

The use of classical cytotoxic chemotherapy in the adjuvant setting appears reasonable in patients with extremely high risk of relapse given the results of the FIRM-ACT trial.[43] In patients with a Ki67 ⩾30% or a large tumor thrombus in the vena cava, cisplatin-based chemotherapy plus mitotane is suggested as an adjuvant option by expert-based consensus, but nevertheless lacks sound scientific evidence.[44] Respective trials are ongoing (Table 1).

Recently, a discussion on the role of adjuvant radiotherapy has been ongoing and is the scope of reviews and meta-analyses.[46,47] Its role is still not exactly clear according to available data, and a recent analysis using the *SEER* database has shown that 10.5% of 865 patients eligible for analysis were given radiation.[46] According to this analysis patients given radiation for stage III node negative ACC had an OS benefit and, also, another analysis (featuring 75 patients) showed that not only loco regional recurrence-free survival, but also that OS might be positively influenced by adjuvant radiotherapy.[47]

Systemic treatment – are we making progress?

Mitotane in advanced disease

Mitotane constitutes the cornerstone of systemic therapy for ACC not only in the adjuvant, but also in the palliative setting. However, mitotane monotherapy resulted in less than 20% overall response rates (ORR) in most series and is thus nowadays usually combined with conventional cytotoxic treatment if the performance status of the patient allows high intensity therapy.[1,48] In the largest publication on mitotane monotherapy including 179 patients with advanced ACC, 26/179 (20.5%) had an objective response, including three cases of complete response, resulting in a median PFS of 4.1 months.[49] The benefit appeared to be more pronounced in patients with low tumor burden and in late onset relapse (i.e. >360 days after initial diagnosis). Again, the target level of 14 ng/ml appeared crucial and resulted in a significantly longer OS for patients above the threshold. Thus, mitotane monotherapy still presents a valid option for patients with low tumor burden not fit for chemotherapy and in the case of predominantly hormone-related symptoms with need for prompt symptomatic treatment. Importantly, mitotane is a strong inducer of CYP3A4,[50] which is of importance for potential combination regimens, especially with novel compounds such as tyrosine kinase inhibitors (TKIs) or immunotherapy. An important question is whether to continue mitotane beyond progression, as no prospective data on this issue are available. In an analysis including 57 long term survivors, defined as >24 months, with slow growing ACC treated with mitotane alone, responses were seen within 12 months, so the authors suggested discontinuation after 12 months if growth of ACC was still observed in this select subgroup of patients.[51] Nevertheless, the common practice in many centers is to keep patients on mitotane as long as tolerance allows, which is also due to the fact that usually no full re-gain of function of the (other) adrenal gland can be expected after discontinuation. However, given novel treatment strategies discussed below, stopping mitotane in terms of interactions and efficacy of subsequent therapies will probably be increasingly applied.

Conventional chemotherapy

Early data on single agent chemotherapy with the anthraycyline doxorubicin resulted in less than 20% ORR, and efficacy of cytostatic monotherapy was only marginally increased if combined with mitotane.[48,52,53] Further single agents tested in combination with mitotane included cisplatin (ORR 30%) and streptozotocin (ORR 36%).[54,55] While cisplatin plus etoposide again showed only modest activity (ORR 11%), the first regimen considered actually effective was the combination of mitotane, cisplatin, etoposide and doxorubicin that was evaluated in an Italian multicenter trial including 28 patients.[56,57] The ORR was promising at 53.5% (95% CI 35–72) and time to progression in responders exceeded 24 months. Based on these findings, the FIRM-ACT study was conceptualized and its results to date are the only positive randomized data for the treatment of advanced ACC.[43] In this investigator-initiated trial, patients with locally advanced or metastatic disease were randomized to receive either mitotane plus streptozotocin (SZ-M) every three weeks, which was considered standard treatment in many centers, or the combination of etoposide, doxorubicin, and cisplatin plus mitotane (EDP-M) every four weeks in the experimental arm. According to protocol, mitotane was started at

Table 1. Clinical trials for adrenocortical carcinoma patients listed as currently recruiting on *ClinicalTrials.gov*.[45]

Drug/intervention	Study title	Setting	Endpoint	Trial design	Pts
Cabazitaxel	Cabazitaxel Activity in Patients With Advanced Adrenocortical-Carcinoma Progressing After Previous Chemotherapy Lines	Relapsed/refractory advanced or metastatic ACC (mitotane stopped 1 month prior to inclusion)	Clinical benefit at 4 months	Single arm phase II	25
Cabozantinib	Cabozantinib in Advanced Adrenocortical Carcinoma	Relapsed/refractory advanced or metastatic ACC (mitotane discontinued, serum concentration <2 mg/L)	PFS at 4 months	Single arm Phase II	37
Cabozantinib	Cabozantinib in Treating Patients With Locally Advanced or Metastatic Unresectable Adrenocortical Carcinoma	Locally advanced of metastatic ACC (mitotane stopped for 1 month, serum concentration <2 mg/L)	PFS at 4 months	Single arm phase II	18
Relacorilant/ pembrolizumab	Study of Relacorilant in Combination With Pembrolizumab for Patients With Adrenocortical Carcinoma With Excess Glucocorticoid Production	Locally advanced or metastatic ACC with glucocorticoid excess (mitotane level ⩽4 mg/L)	ORR, dose-limiting toxicities	Phase Ib	20
Therapeutic vaccine (EO2401)/nivolumab	A Novel Therapeutic Vaccine (EO2401) in Metastatic Adrenocortical Carcinoma, or Malignant Pheochromocytoma/Paraganglioma	ACC locally advanced or metastatic (also including pheochromocytoma or paraganglioma)	Safety	Phase I/II	60
Nivolumab/ipilimumab	Nivolumab Combined With Ipilimumab for Patients With Advanced Rare Genitourinary Tumors	Locally advanced or metastatic ACC (mitotane allowed for control or endocrine symptoms) and other rare genitourinary tumors	ORR	Single arm phase II	100*
Nivolumab/ipilimumab	Nivolumab and Ipilimumab in Treating Patients With Rare Tumors	Relapsed/refractory advanced or metastatic ACC or other rare tumors	ORR	Single arm, phase II	818*
Pembrolizumab	Pembrolizumab in Treating Patients With Rare Tumors That Cannot Be Removed by Surgery or Are Metastatic	Relapsed/refractory advanced or metastatic ACC or other rare tumors	Non-progression at 27 weeks, adverse events	Single arm phase II	225*
HIPEC (cisplatin and sodium thiosulfate), cytoreductive surgery	Surgery and Heated Intraperitoneal Chemotherapy for Adrenocortical Carcinoma	ACC with the majority of disease confined to the peritoneal cavity and resectable or amenable to radiofrequency ablation	PFS	Single arm phase II	30
Cisplatin/etoposide +/– mitotane *versus* observations or mitotane	Adjuvant Chemotherapy *versus* Observation/ Mitotane After Primary Surgical Resection of Localized Adrenocortical Carcinoma	Adjuvant setting following complete resection for ACC with Ki67 ⩾10%	RFS	Open-label, randomized phase III	240
Cisplatin/ etoposide + mitotane *versus* mitotane	Mitotane With or Without Cisplatin and Etoposide After Surgery in Treating Patients With Stage I–III Adrenocortical Cancer With High Risk of Recurrence	Adjuvant setting following complete resection for ACC with Ki67 >10%	RFS	Open-label, randomized phase III	240

*These numbers include also other tumor entities.
Date of website access 19 May 2021; search terms included "adrenocortical carcinoma" & "adrenal cancer" & "recruiting" (excluding registry studies, observational studies and pediatric studies).
ACC, adrenocortical carcinoma; ORR, overall response rate; PFS, progression-free survival; Pts, patients; RFS, relapse-free survival.

least 7 days before cytotoxics, aiming for 14–20 mg/L blood level during therapy; the median measured level, however, was only around 5 mg/L in both groups. Patients were randomized 1:1 with 151 patients in the EDP-M arm and 153 in the SZ-M-arm. The primary endpoint was OS, secondary endpoints were response rate and progression free survival (PFS). The ORR was superior for EDP-M with 23.2% *versus* 9.2% for SZ-M ($p < 0.001$), which was much lower than in initial phase II trials on SZ-M. The median PFS of 5 months for EDP-M was significantly prolonged *versus* 2.1 months for SZ-M, while the actual 1-year PFS of 26.1% *versus* 7.2% is still disillusioning. In addition, the OS did not reach statistical significance with 14.8 *versus* 12 months (HR 0.79, 95% CI 0.61–1.02), but there was a crossover integrated in the protocol, so a total of 101 patients received second line therapy with EDP-M, resulting in a similar outcome to first line of 5.6 months PFS. The FIRM-ACT protocol is therefore the current standard of care for advanced ACC. However, the medians PFS of <6 months and the OS of roughly 1 year clearly indicate a high unmet need for improvement, as in fact no recent chemotherapy-based trials have suggested positive trends. Second line or salvage chemotherapy regimens show only marginal efficacy, and include gemcitabine plus capecitabine (either conventional or with metronomic dosing), which is most commonly used in our personal practice, and single agents such as thalidomide or trofosfamide, which were both evaluated in German centers but again resulted in stabilization rates of only <15%.[58–61] In addition, combinations of gemcitabine with erlotinib or bevacizumab and capecitabine were evaluated but were considered not of clinical relevance.[62,63]

TKIs and other targeted therapies

TKIs targeting one or more tyrosine kinases involved in proliferation of tumor cells and other small molecule therapies have been effectively established as standard in several (neuro) endocrine cancers, including sunitinib and everolimus for pancreatic neuroendocrine tumors, and cabozantinib, vandetanib, sorafenib and lenvatinib for different subtypes of thyroid cancer.[64,65] However, while various pathways and growth factors, for example, IGF-II, VEGF, FGF II and TGF-α/-β, have been attributed preclinical relevance in ACC growth,[66] no mono-therapeutic small molecule inhibitor has shown convincing activity so far. Among others, sunitinib, gefitinib, erlotinib, sorafenib and temsirolimus were evaluated in small series but resulted in only modest response rates.[67] One potential reason discussed is an altered metabolism due to mitotane-induced CYP3A4 activity for some compounds. CYP3A4 induction and interaction in TKIs was incidentally observed in sunitinib treated patients, where concomitant mitotane negatively impacted outcome due to lower serum levels of active metabolites, and is now understood as an important bias to consider in all clinical trials;[50,68] particularly as even after stopping mitotane it still can influence pharmacokinetics due its long-half life with often residual activity beyond termination. Interestingly, concomitant mitotane did not lead to alteration of toxicities in the sunitinib trial but also this needs to be considered.[68] Contemporary clinical trials provide strict in-/exclusion criteria regarding concomitant use of mitotane.

One potential promising strategy was targeting the IGF-2-axis, which is considered the most commonly overexpressed molecule in ACC and is involved in proliferation, migration and development of metastases.[69] Based on preclinical data, IGF-2 expression results in IGF-1R and insulin receptor activation and phase I studies involving inhibitors of IGF-R1 showed promising results in terms of potential antitumor activity. Linsitinib, a specific inhibitor of IGF-R1 and the insulin receptor, was evaluated with great efforts in an international randomized phase III study enrolling a total of 139 patients who had progressed on standard chemotherapy. Severe adverse events were rare with fatigue, nausea and hyperglycemia reported in <5% as grade 3+ events. The trial was, however, unblinded early due to failure of endpoints, with no difference in PFS or OS observed (OS median 323 days for linsitinib and 356 days for placebo, HR 0.94). While mitotane levels had no influence on the pharmacokinetics of linsitinib in this study, the author hypothesized that more specific knowledge on the distinct patients' genetic profiles might allow tailored use of such inhibitors. In addition, combination partners such as mTOR inhibitors appear attractive and recent *in vitro* data support this concept as an additive effect of mTOR inhibitors to linsitinib was observed.[70] A phase I expansion cohort study investigated IGF-R1 antibody cixutumumab plus temsirolimus in 26 patients, resulting in disease stabilization for more than six months in 42%.[71] Cixutumumab combined with mitotane was assessed as upfront treatment in patients with unresectable recurrent or metastatic disease.[72] Disease control was

achieved in 8/20 patients but median PFS was 6 weeks only and a planned randomized expansion phase was not started owing to slow accrual and limited efficacy. Furthermore, monotherapy with mTOR inhibitors including everolimus, sirolimus and temsirolimus was evaluated based on the fact that the mTOR pathway is a known regulator of insulin like growth factors, but so far available results include only cell culture data or small clinical series.[73,74] Another TKI that deserves attention is cabozantinib, an inhibitor of VEGFR2, MET and RET approved for several tumor entities including positive phase III results in medullary thyroid cancer.[75] In a recently published retrospective series, a total of 16 patients following previous mitotane and further systemic therapies were treated with cabozantinib.[76] ORR was 19% with a disease control rate of 50% and, importantly, mitotane was out of relevant plasma levels in all patients (discontinued prior treatment in all patients, >12 months in 6/16). Corresponding phase II studies are recruiting, and again mitotane discontinuation is an important prerequisite to prevent potential interactions (Table 1). EGFR and VEGFR inhibition in combination with TKIs or classical cytostatic therapy has also been evaluated, but did not relevantly improve outcomes.[44,77] In summary, multiple targeted therapies including also further TKIs (e.g. sorafenib, lenvatinib, axitinib, nilotinib) and targeted antibodies (e.g. figutumumab), alone or in combination (e.g. with immunotherapy), have been evaluated for ACC.[49,78–82] Targets and pathways still open for clinical exploration include the Wnt/beta-catenin signaling pathways; SF-1, as commonly over regulated transcription factor; ACAT1, an enzyme involved in the cholesterol metabolism and initially investigated for cardiovascular disease but displaying significant adrenal toxicities; the estrogen pathway, as well as FGR inhibitors.[67,77] Some experts have suggested that in view of the low efficacy of EDP-M, upfront targeted therapy should be discussed if a new drug or target is available, followed by EDP-M in the case of progression only.[44]

Immunotherapy

Tumors of endocrine organs in general and ACC in particular are considered immunologically cold with PD-L1 expression reported in 10% of ACC, low to intermediate levels of tumor mutational burden in most patients and <5% microsatellite instability high (MSI-H) patient proportions.[83] However, while the first larger immunotherapy study investigating avelumab in a phase Ib expansion cohort of 50 patients with advanced ACC was rated negative due to an ORR of 6% only and a median PFS of 2.6 months, a recent phase II study on pembrolizumab has shown a first positive sign for checkpoint inhibitor activities in ACC.[84,85] In this phase II trial, 39 patients with advanced ACC were treated with pembrolizumab at a standard dose of 200 mg every 21 days.[85] The reported ORR of 23% (95% CI 11–39) and the disease control rate of 52% (95% CI 33–69) appear clearly higher than in the avelumab trial. While the median PFS was again low at 2.1 months (95% CI 2–10.7), the median duration of response with a lower CI of 4.1 months (to not reached) and the OS of 24.9 months (95% CI 4.2 months to not reached) suggested durable activity in some patients. Interestingly, response did not correlate with PD-L1 expression or microsatellite instability/mismatch repair deficiency status. Further evidence regarding pembrolizumab derived from a pre-specified cohort of a phase II from the MD Anderson Cancer Center, where 16 progressive ACC patients were treated with pembrolizumab.[86] The primary endpoint of non-progression at 27 weeks was achieved in 36% (95% CI 13–65); the disease control rate in this study was 56% and the authors assessed tumor-infiltrating lymphocytes (TILs), which again did not correlate with response. Nivolumab showed only modest activity in 10 patients (multicenter phase II) with a median PFS <2 months.[87] It must be considered that mitotane protocols were different, with concomitant therapy allowed in the avelumab study, but not in the pembrolizumab trials.[84–86] Furthermore, endocrine activity may have an impact as particularly hypercortisolims can complicate immune response and detection of adverse effects in patients treated with checkpoint inhibitors.[83,88] Also, *CTNNB1*/beta-catenin overexpression, which is frequently found in ACC, is potentially relevant as *CTNNB1* activity was associated with immune exclusion (and increased cortisol production).[89] Additionally targeting *CTNNB1* might be a potential way to increase checkpoint inhibitor efficacy.

To date, the situation of immunotherapy for ACC remains unclear. Clinical response rates still lack major breakthrough success and the tumor microenvironment, which is of importance for response and resistance patterns to this kind of therapy, appears particularly complex. One key point is the impact of corticosteroid-induced immune cell depletion, causing lower numbers of

circulating lymphocytes, and a high load of T-cell suppressive CD276 (B7-H3), in addition to low levels of classical biomarkers for immunotherapy including PD-L1, tumor mutational burden (TMB), TILs and MSI-H.[83,90] Other factors discussed as mechanisms of resistance to immunotherapy in ACC are alterations in the WNT–beta-catenin pathway that cause changes to the CD8+ population in the tumor microenvironment and alter the specific immune response.[90] Furthermore, TP53 inactivation can decrease production of cytokines necessary for immune effector cell invasion. However, based on the given data, immunotherapy may be applied in selected patients if available – not least due to the sobering results of chemotherapy-based salvage regimens. The best evidence currently available is probably for pembrolizumab at standard dosing of 200 mg every three weeks. This is also highlighted in a recent review summarizing efficacy and toxicity for a total of 115 ACC patients treated in prospective trials with immunotherapy.[91] The combination of nivolumab plus ipilimumab might be interesting and a trial is ongoing (Table 1). Novel immunotherapeutic approaches not yet extensively assessed include autologous dendritic cell vaccinations or targeting further immune checkpoints such as CD276 (B7-H3).[83]

Personalized treatment concepts

A series assessing drugable molecular alterations in 107 patients using NGS reported that at least one target of interest was found in 60% of patients ($n=64$). The most frequent finding was copy number variations of *CDK4* genes in 43% of patients that can be targeted by CDK4/6 inhibitors.[92] Moreover, alterations in *NOTCH1*, *NF1* and *MDM2* were suggested as potential targets. A comparable study found relevant targets in only 16% of patients, if Food and Drug Administration approved drugs were assessed and corresponding compounds again included CDK 4/6 inhibitors, but also PARP inhibitors, MEK or ERK inhibitors and PI3K/Akt/mTOR inhibitors.[25] As an interesting co-finding, profiles of primary tumors and metastases were compared and were not reported to be substantially different. Given the increasing availability and simplicity of NGS on archived FFPE tissues, precision medicine approaches appear of interest and will potentially allow to more specifically tailor treatment of selected ACC patients in the near future. A restriction to this might be the time needed for NGS data to be completed. At our own center, in a preliminary series of 10 patients no relevant targets were detected by use of a broad NGS panel.[93]

Is there a role for image guided therapy and theranostics?

Chemokine receptor expression has been suggested as a relevant target for diagnostic and therapeutic purpose in a variety of tumor entities and both CXCR4 and CXCR7 were detected at relevant levels in ACC patients with localized or advanced disease, potentially offering options for CXCR4-directed treatment.[94,95] In addition, antagonizing CXCR4 was able to block immune escape mechanisms to immunotherapy in other solid tumors. Very recently, also the role of somatostatin receptor (SSR) expression was assessed, and strong uptake suggesting eligibility for yttrium-90/lutetium-177 DOTATOC peptide receptor radionuclide therapy (PRRT) was found in a small proportion of patients (2/19).[96] In these two patients, PRRT was performed and resulted in durable responses. Given the high evidence regarding safety and efficacy in other SSR-expressing tumors of neuroendocrine origin, this concept appears of interest for further assessment. Another concept is the use of [123I]metomidate for targeted radionuclide therapy in ACC.[97] However, only small case series have been published so far for both tracers.

Conclusion

Prognosis of advanced ACC is still limited. Chemotherapy following the FIRM-ACT protocol constitutes standard of care and while TKIs and other targeted therapies suggest potential activity, there is a clear need for novel therapeutic concepts and clinical trials. Recent advances in understanding the molecular profile of ACC underline the high complexity of this disease, which is – apart from limited drugable molecular targets – characterized by a complex interplay of a yet scarcely understood microenvironment and potential endocrine activity. Particularly steroid-excess further complicates therapeutic concepts such as immunotherapy, which have markedly improved outcome in other disease entities. In Table 1, we display clinical trials listed as currently recruiting on *ClinicalTrials.gov* and we strongly encourage inclusion in trials whenever possible, as only this will allow for true progress in handling ACC. Given the rarity of this disease, this also asks for active international collaborations and optimal inter-disciplinary communication.

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