

Adrenocortical carcinoma

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Chapter 09

Impact paragraph

Adrenocortical carcinoma (ACC) is a rare type of cancer. This thesis focuses on the identification of markers that could improve the accuracy of diagnosing, treating, and estimating survival of ACC.

Survival

In **chapter 2** of this thesis it is concluded that patients who develop metastases within six months after initial diagnosis of ACC have a more poor overall survival (OS) than patients with metachronous metastasis. Also, patients with a high disease burden at diagnosis, four or more metastases or two or more affected organs, have a more grim overall survival than patients with limited disease. Furthermore, it is suggested that surgery might have a positive impact on OS for patient with synchronous metastases. In **chapter 3** a prediction model for ACC specific mortality is proposed. The model is based on age, modified European Network for the Study of Adrenal Tumors (mENSAT) stage, and radical resection.

ACC has a heterogeneous prognosis. Studies have been published describing aggressive stage III ACC, biologically behaving like stage IV, but also stage IV patients with exceptional long survival. This emphasizes that the biological heterogeneous behavior of ACC is not fully captioned with ENSAT stage. Therefore, there is a need for better prognostication in ACC to inform the individual patient on survival and assist in deciding on treatment strategy. The impact of **chapter 2** and **3** is the addition of information on ACC prognosis, to better capture the biologically heterogeneous behavior of ACC, not fully endorsed by the ENSAT stage. We hope that this new information will support the implementation of mENSAT in the ACC guideline. Better staging may encourage earlier, for example, surgical intervention through defining of (severe) prognosis, and may support further research into surgery in advanced ACC.

The information on prognostication is relevant for both ACC patients as well as their caregivers. Our research has been published and has been presented at national and international congresses.

If, in the future, our study outcomes will be implemented in daily practice it would be relevant to inform patients, for example using online platforms (international Facebook patient groups, accsupport.org.uk etc.).

Treatment

Mitotane is a keystone in the treatment of ACC. It is used both in adjuvant setting as well as in patients with metastatic disease. Mitotane has a small therapeutic window of 14-20 milligram per liter. Survival benefit has been proven in patients with blood

levels higher than 14mg/L whereas blood levels higher than 20mg/L are associated with increased toxicity. Toxicity is primarily gastro-intestinal and neurological and even leads to temporary or final discontinuation of mitotane therapy in some cases.

There is a large inter-patient variability in reaching and maintaining therapeutic concentrations, without a clear relationship between the mitotane dose and the serum concentration. The build-up of the therapeutic plasma concentration is in general slow. In most patients this level is reached after three months of treatment with a daily dose of about 6.0 gram (12 tablets of 500 milligrams). This means a delay of the optimal therapeutic effect. This complicates timing of therapy evaluation and consequently, the decision to add cytotoxic chemotherapy to the treatment.

Dosing regimens are based on clinical experience and adjusted according to plasma concentration and tolerability. The inability to predict mitotane levels leads to relative under dosing and a prolonged build-up phase in some patients, while others unexpectedly demonstrate high plasma levels early in therapy, causing increased toxicity. Earlier it was shown that there are only weak correlations between weight, age, gender, height and the pharmacokinetics of mitotane. The main goal in **chapter 4** was identifying pharmacogenetic differences among patients treated with mitotane by analyzing genes related involved in drug absorption, distribution, metabolism and elimination (ADME). In **chapter 4** it is shown that pharmacokinetics of mitotane can partially be explained by pharmacogenetics: a two compartment pharmacologic model is presented best describing the population pharmacokinetic (PK) data of mitotane. Lean body weight (LBW), genotypes of CYP2C19*2 (rs4244285), SLCO1B3 699A>G (rs7311358), and SLCO1B1 571T>C (rs4149057) were identified to affect mitotane clearance (CL/F) significantly.

The developed model is beneficial to optimize mitotane treatment schedules and to guide the initial dose selection for patients. Therefore it is relevant for ACC patients starting with mitotane therapy.

Currently only half of the patients treated with mitotane reach therapeutic levels and up to 50% of patients discontinue treatment because of toxicity. Our pharmacokinetic model could assist optimization of mitotane dosage to guide the build up to a therapeutic level, but prevent overshooting to toxic levels.

The model needs to be externally validated: it needs to be tested with a different set of patients to see if the results of our study can be generalized to and across other patients in different contexts.

If validated we would encourage the use of an online resource to make our model available worldwide for experts who treat ACC patients. The shiny app could for example be implemented in the ENSAT website.

Orphan disease

Adrenocortical carcinoma is an orphan disease. There are multiple definitions of orphan disease: it has been used to describe diseases that are neglected by doctors, or used to designate diseases that affect only small numbers of individuals and as disease that has not been adopted by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it. It defines a large group of diseases which are characterized by a low prevalence in the population. They frequently are associated with problems in diagnosis and treatment.

In **chapter 5** foreseen changes in diagnostic and prognostic instruments are discussed and suggestions are made for clinical management and possibilities for future treatment of ACC.

It has been proven repeatedly that the establishment of (inter)national collaborative networks of expert centers has a favorable effect on survival of ACC patients. Because of ACC being an orphan disease, we suggest that quality criteria other than volume criteria might be of greater importance: it seems more important that centers adhere to treatment as suggested in up to date guidelines, which in turn seems best feasible in a specialized centers with dedicated physicians. Furthermore, these international collaborative networks, such as ENSAT, encourage clinical trials. By working together sufficient patient numbers can be provided in order to achieve adequate reductions in uncertainties about e.g. treatment effects and run those clinical trials to test new treatment possibilities that are so badly needed. The impact of **chapter 5** is that it goes against current ideology of treating cancer patients in high-volume facilities. It endorses the treatment of ACC with mitotane by experts, even if this means treatment in low volume centers. It encourages initiatives as the European Network for the Study of Adrenal Tumors (ENSAT) and the A5: American–Australian–Asian Adrenal Alliance. It is a plea for collaboration even in the current competitive scientific culture where the credo seems to be ‘to publish or perish’.

Many of the suggestions made in **chapter 5** (additional prognostic factors are needed; a uniform methodology for assessing the Ki-67 index in ACC needs to be established; centers should adhere to current state-of-art treatment concepts which seems best feasible in a specialized centers with dedicated physicians, adequate supportive treatment during mitotane therapy cannot be stressed enough; international collaboration is necessary to facilitate fundamental research and clinical trials to test new treatment possibilities) are included in the European guideline published in 2018, for example the recommendation that the pathology report should at least contain Weiss score (including the exact mitotic count), exact Ki67 index, resection status and pathological tumor stage (indicating invasion or not of the capsule and/or surrounding tissue and organs) and nodal status.

Also, **chapter 5** has been cited for at least 14 times by other scientific authors.

Epigenetics

Adrenocortical carcinoma occurs both as an inherited form of cancer as well as a sporadic neoplasm, being prominent in the Brazilian population.

Inherited ACC, associated with familial syndromes, as well as the increased incidence in the Brazilian population is associated with a mutation in TP53, a gene that codes for a protein that regulates the cell cycle and hence functions as a tumor suppression. In sporadic ACC a TP53 mutation is often lacking.

Overall, the understanding of the pathophysiology, especially genetic cause, of ACC is limited. Mutations in insulin-like growth factor 2 (IGF2), β -catenin (CTNNB1 or ZNRF3), and TP53 have been associated with ACC. So, if the usual mutation analysis doesn't explain the familial cause, how can we solve the conundrum of how ACC develops? The answer might be epigenetics.

Epigenetic alterations occur in cancer cells as commonly as genetic mutations and have the ability to mimic the effects of the latter. Therefore, epigenetics are currently an increasing interest in the subject of cancer research. Epigenetics refers to the non-sequence-based modifications of DNA or its associated factors (e.g., histones) that are maintained during cell division. Most epigenetic changes concern DNA methylation, attaching methyl groups to segments of DNA, and histone modification. Hypermethylation is a common phenomenon seen in cancer. Studies suggests that epigenetic alterations precede tumor formation and increase the probability of cancer when genetic changes arise instead of being the consequence of tumor progression. Understanding the methylation process in adrenal tumours could expand our knowledge of tumorigenesis and improve current therapy strategies providing potential drug targets.

Chapter 6 summarizes recent findings on epigenetics of ACC and its role in diagnosis, prognosis and therapeutic strategies.

Different studies are presented who have been able to show clustering on epigenetic level, allowing differentiation based on these specific epigenetic findings not only between benign and malignant adrenals tumors, but also correlate with ACC aggressiveness. Therefore, epigenetics is suggested a significant addition to current histological parameters. Moreover, it might serve as an addition to current ENSAT staging in order to estimate prognosis and tumor aggressiveness. In **chapter 6** suggestions are made for follow up research, stimulating the implementation of a reproducible epigenetic (cluster) biomarker in the guideline. Also, a new flowchart on the potential management of the adrenal mass with the implementation of genomic analysis is presented.

The addition of a well reproducible biomarker would be of significance, where current diagnostic and prognostic markers occasionally are unable to differentiate (borderline) malignant from benign and insufficiently correlate with biological behavior of ACC.

Chapter 6 could form the base of which in the future a study protocol could be proposed to prospectively compare the pathologic classification (Ki67 and Weiss score) of adrenal tumors versus a genomic assay versus the combination of both (PA vs genomics vs PA + genomics) in the process of accurately diagnosing adrenal tumors.

Personalization

The impact of this thesis in general, is that it attempts to individualize diagnosis, prognostication and treatment of ACC. Health professionals are often uncomfortable with prognostic uncertainty but the process of addressing “what to expect” for an individual’s disease course is essential for meaningful decision-making and end-of-life planning. Additional information on prognostication as provided in this thesis could support such conversation. The same goes for tailoring of treatment. A professional should explore: does the patient strive for quantity of life or quality of life? In the process of shared decision making, patients are required to make trade-offs between the two. Some patients are willing to endure toxicities associated with treatment in order to increase their length of life, while others value quality more and are reluctant to spend their remaining years in a compromised state. This involves weighing the risks and benefits of treatment and managing the patients’ expectations and concerns. In order to do so international effort needs to be made to investigate ACC patients experience with the diagnostic process and treatment of ACC and study patient reported outcomes, which are currently scarce for ACC. Furthermore, international collaborative research should continue to invest in the optimization of current- and development of new ACC treatment.