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REVIEW

Adrenocortical carcinoma

C.I.M. van Ditzhuijsen, R. van de Weijer, H.R. Haak*, on behalf of the Dutch Adrenal Network

Department of Internal Medicine, Máxima Medical Centre Eindhoven, Ds. Th. Fliednerstraat 1, 5600 PD Eindhoven, the Netherlands, tel: +31 (0)40-888 52 97, *corresponding author: e-mail: H.Haak@mmc.nl.

ABSTRACT

Adrenocortical carcinoma is a rare disease with a poor prognosis. Patients can present with a hormonal syndrome or with general symptoms from an abdominal mass. The pathogenesis is unknown. Sometimes the adrenocortical carcinoma is associated with tumour syndromes such as the Beckwith-Wiedemann and Li-Fraumeni syndrome; however, most tumours are sporadic. Using one of the international classification methods, histopathological research can in almost all cases distinguish between adrenocortical adenoma and carcinoma. Complete surgical resection is the treatment of choice for adrenocortical carcinoma. Mitotane is given when surgery is not possible, after incomplete resection or for metastatic disease. Frequently used chemotherapeutic combinations are etoposide, doxorubicin, cisplatin and mitotane (EDP/M) and streptozotocin and mitotane (Sz/M). International and national cooperation has resulted in a randomised trial aimed at determining a standard therapy in advanced adrenocortical carcinoma. The Dutch Adrenal Network is a national cooperation of endocrinologists, pathologists and oncologists from all eight academic centres and Máxima Medical Centre. The network combines knowledge and expertise and gives patients the opportunity to receive optimal treatment in their own district.

KEYWORDS

Adrenocortical carcinoma, therapy, treatment

INTRODUCTION

Adrenocortical carcinoma is a rarely occurring disease. The annual incidence is approximately 1-2 individuals per million.[1] The poor prognosis and the scant knowledge and experience of physicians pose a major problem for both physicians and patients. Therefore, it is important to centralise knowledge of and experience with adrenocortical carcinoma, so that patients get the best possible treatment and care.

This article reviews new developments in both treatment options and national/international cooperation for patients with adrenocortical carcinoma. First the clinical features, diagnostics, pathology and pathogenesis of adrenocortical carcinoma will be discussed, followed by treatment options and a description of national and international cooperation and the related trials.

Finally the Dutch Adrenal Network will be discussed, which aims at optimalisation of treatment and care of patients with adrenocortical carcinoma in the Netherlands.

CLINICAL PRESENTATION

Approximately 60% of adrenocortical tumours are hormonally active. Cushing's syndrome alone or a mixed Cushing's syndrome with virilisation is the most frequent presentation.[1-3] This can be a rapidly developing disease with skin atrophy, hyperglycaemia, muscle weakness, hypertension and psychiatric disorders. Androgen-secreting adrenocortical carcinoma presents with male pattern baldness, low voice, hirsutism and oligoamenorrhoea in women. Oestrogen-secreting tumours present with gynaecomastia and testicular atrophy in males.[4]

Hyperaldosteronism, characterised by hypokalaemia and hypertension, may also be present.[5] However, severe hypokalaemia can also be caused by elevated cortisol secretion.

Patients with a hormonally inactive adrenocortical carcinoma often present with local symptoms of the tumour itself, including abdominal fullness, pain and gastrointestinal complaints such as nausea and vomiting.[5]

Adrenocortical carcinomas are increasingly detected as an incidentaloma during abdominal imaging. A minority present with fever and weight loss and in a few cases a palpable mass can be felt on physical examination.

Adrenocortical carcinoma tends to spread by both the haematogenous (most frequently the lungs, followed by the liver and sometimes the bones), and the lymphogenous route (to regional and paraaortic lymph nodes).[6] Metastases to the other adrenal, or bilateral adrenocortical carcinoma, may be found in 4% of the cases.[7]

PROGNOSIS AND STAGING

Stage 1 and 2 describe tumours of less or more than 5 cm, respectively. Stage 3 describes locally invasive tumours or tumours with regional lymph node involvement. Tumours invading adjacent organs or tumours with distant metastasis are categorised as stage 4.[7]
The average survival time of untreated patients is 2.9 months and largely depends upon the tumour size.[8] With treatment the five-year survival rates are 60% for stage 1, 58% for stage 2, 24% for stage 3, and 0% for stage 4.[9]

DIAGNOSTIC EVALUATION

The diagnostic evaluation of adrenocortical carcinoma depends upon the clinical presentation. Cushing's syndrome at time of presentation requires measurement of the urinary cortisol excretion for 24 hours, early morning cortisol after 1 mg dexamethasone at 23.00 hours the night before (known as the 1 mg overnight suppression test), or the late night (salivary) cortisol level. A positive (elevated) result of one of these tests confirms Cushing's syndrome. Low levels of plasma ACTH are seen with the ACTH-independent, adrenal variant of Cushing's syndrome.[10]
Gas chromatographic separation of 17-ketosteroids reflects an abnormal steroidogenesis which is characterised by increased levels of cortisol precursors such as 17-OH-progesterone and 17-OH-pregnenolone. An abnormal gas chromatography with excess excretion of the cortisol precursors establishes the clinical diagnosis of adrenocortical carcinoma.
Elevated plasma levels of dehydroepiandrosterone sulphate (DHEAS) and testosterone in women and 17-β-oestradiol in men are markers for adrenocortical carcinoma, although their specificity is unknown.[11]
CT scan or MRI is the best diagnostic procedure for patients presenting with pain or a palpable tumour at physical examination.[5] On CT scan or MRI benign and malignant disease can be distinguished based upon the size, irregularity and inhomogenicity. However, in the end, adrenocortical carcinoma is a histological diagnosis.
In 30% of adrenocortical carcinomas calcifications are visible. Adrenocortical lesions with a density of more than 10 Hounsfield units on a non-contrast CT scan, or less than 50% washout of contrast after 15 minutes together with a density of more than 35 Hounsfield units, are suspect for malignant tumour.[7] FDG-PET scan can detect locoregional tumours and metastatic disease.

PATHOLOGY

At the time of clinical presentation it is difficult to differentiate between benign and malignant disease unless evidence of metastatic disease is present. Several histopathological characteristics are useful for differentiating benign from malignant disease. There are two important classification systems by von Weiss and van Slooten, respectively. In the Netherlands the classification by van Slooten is usually used. Internationally the Weiss score is the most widely used tool.[12-14] The classification by van Slooten is based upon the following parameters: regressive nature, conservation of normal histology, nuclear atypia, nuclear hyperchromasia, structure of nucleoli, mitotic activity and capsular invasion.[12] The mitotic activity is the most important parameter.
Tumour markers such as Ki-67, inhibin, melan-A and calretinin are detected with immunohistochemical examination; however, they have a low specificity for adrenocortical tumours.

PATHOGENESIS

The aetiology of adrenocortical carcinoma is mostly unknown, as are the risk factors. Sporadic adrenocortical carcinoma is most common; however, hereditary syndromes do occur as in the Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, Carney complex, MEN-1 syndrome and McCune-Albright syndrome.[15,16] The Li-Fraumeni syndrome is caused by inactivating mutations of the p53 tumour suppressor gene.
The gene defect responsible for the Beckwith-Wiedemann syndrome is localised on the 11p5.5 locus and leads to tumours such as Wilms tumours, neuroblastoma, hepatoblastoma and adrenocortical carcinoma. The 11p5.5 locus contains the IGF-II, H19 and the p57/Kip2 genes, the last one coding for the p57 tumour suppressor protein.[17] ACTH receptor mutations are not important in the pathogenesis of adrenocortical carcinoma. The role in the carcinogenesis of decreased ACTH response is unclear.

THERAPY

Surgery

The best treatment for adrenocortical carcinoma is complete resection of the tumour. The overall five-year survival rate after total resection is 49%, in contrast to

9% after incomplete resection.[18] When total resection is not possible, debulking is a therapeutic option to decrease excess hormone production, and is possibly associated with a better overall survival compared with nonsurgical treatment. Resection of recurrent disease is advised because of the increased overall survival.[5]
The risk of capsular damage is the same for malignant and benign tumours; however, it increases with laparoscopy. This is more of a problem for malignant tumours because the spill of malignant cells may result in the development of metastasis.

Mitotane
Mitotane is the treatment for inoperable tumours, metastatic disease and after incomplete resection.[18] Mitotane is an isomer of the insecticide p,p'-DDD and chemically related to insecticide DDT. Its cytotoxic effect on the adrenocortical cells leads to necrosis of the fascicular and reticular zone. Metabolic activation is necessary for its adrenolytic effect. Adrenal steroidogenesis is also impaired by the inhibitory effect on steroidogenic enzymes.[19]
Mitotane is given as tablets (Lysodren). Mitotane leads to tumour regression in 27% of the patients with advanced adrenocortical carcinoma and to control of hormone excess in the majority of patients.[7] Objective tumour response was found only among patients with a mitotane level of more than 14 mg/l.[18,19]
The therapeutic plasma levels vary between 14 and 20 mg/l, measured at least 12 hours after the last ingestion with an initial measurement after 14 days. The initial dose of mitotane is 1.5 g/day, rapidly increasing to 5 to 6 g/day depending on the patient's tolerance of the drug. The dose is adjusted according to the mitotane plasma concentration and tolerability. Plasma levels above 20 mg/l can lead to serious side effects probably without enhancing the effectiveness. Possible side effects are gastrointestinal symptoms (nausea, vomiting, diarrhoea, anorexia), neurological symptoms (insomnia, confusion, depression, tremor, ataxia) and a prolonged bleeding time due to platelet dysfunction.[20] Additional side effects can occur due to adrenal insufficiency and elevated plasma steroid-binding capacity. Therefore, hydrocortisone and fludrocortisone substitution, in high doses, is necessary. The exact dose is determined by the clinical condition, blood pressure and laboratory parameters (Na, K, ACTH).[18]
After total regression, mitotane is continued for one to two years. With persisting, stable disease mitotane can be continued lifelong, or as long as considered necessary.

Chemotherapy
The choice of chemotherapy in the treatment of adrenocortical carcinoma is based on small trials (*table 1*). No prospective randomised trials are available because of the low incidence of adrenocortical carcinoma.
Berruti *et al.* showed that the combination of etoposide, doxorubicin, cisplatin and mitotane is a therapeutic option in advanced adrenocortical carcinoma.[21] Kahn *et al.* showed positive results with the streptozotocin and mitotane.[22]

INTERNATIONAL COOPERATION: TRIAL

The international consensus conference on adrenal cancer, in Ann Arbor, USA in September 2003, recommended both etoposide, doxorubicin, cisplatin in combination with mitotane, and streptozotocin in combination with mitotane as therapeutic options in advanced adrenocortical carcinoma.
As a result of this conference the Collaborative Group for Adrenocortical Cancer (COACT) has been set up. The COACT has taken the initiative to start a large

Table 1. *Overview of studies for cytotoxic chemotherapy for adrenocortical carcinoma*

Cytotoxic compound	Mitotane	n	CR (n)	PR (n)	Total (%)	Reference
I	-	12	-	-	0	18
P, E	-	45	-	5	11	19
D, V, E	+	35	1	4	14	20
C, D, P	-	11	-	2	18	21
D	-	16	1	2	19	22
D, P, 5-FU	-	13	1	2	23	23
P	+	37	1	10	30	24
P. E	+	18	3	3	33	25
S	+	22	1	7	36	26
P, E	-	13	-	6	46	27
E, D, P	+	28	2	11	54	28
		250	10	52	25	

I=irinotecan, D=doxorubicin, E=etoposide, 5-FU-5fluorouracil, C=cyclophosphamide, V=vincristine, S=streptozotocin, P=cisplatin, CR=complete response, PR=partial response.

international study: FIRM ACT (First International Randomised Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment). A multicentre cooperation is the only way to implement this trial. It is a phase III, randomised, open-label, cross-over trial, with the Netherlands, Sweden, Italy, Germany, France, United States and Australia participating. The FIRM-ACT trial compares etoposide, doxorubicin, cisplatin and mitotane (EDP/M) with streptozotocin and mitotane (Sz/M), in order to determine a standard therapy for advanced adrenocortical carcinoma (*figure 1*). The total duration of the trial will be seven years, five of which will be for trial inclusion. In total 300 patients will be randomised. The most important inclusion criteria are histologically confirmed diagnosis and a stage III-IV metastatic disease.

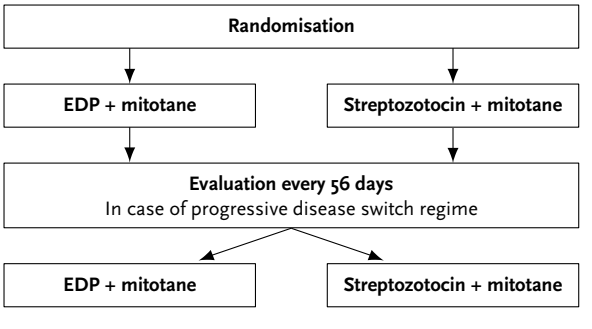
During the treatment with EPD/M, four days of chemotherapy is administered every four weeks. On the first day doxorubicin 40 mg/m^2 is administered, followed by three days of etoposide 100 mg/m^2, the last two days in combination with cisplatin 40 mg/m^2.

In the first five days of the Sz/M scheme streptozotocin 1g is administered daily, followed by 2 g/day during the next 21 days. In both groups mitotane is administered daily, with a plasma level between 14 and 20 mg/l. Mitotane is started at least two weeks before starting the other chemotherapy.

The primary endpoint is whether the EDP/M regimen prolongs overall survival compared with Sz/M. Secondary endpoints are the quality of life, time to progression, time till response and total response duration of the disease. The relation between the plasma levels of mitotane and the overall survival will be determined for both treatment groups.

In case of unacceptable toxicity or progression of the underlying disease, patients will be treated according to the treatment regime of the other group, so that second-line treatment data will become available for both treatment regimes.[23]

Figure 1. *Randomisation regimen in the Firm-ACT trial*



NATIONAL COOPERATION: THE DUTCH ADRENAL NETWORK

The Dutch Adrenal Network was set up in 2004 as a national cooperation of endocrinologists, pathologists and oncologists from all (eight) academic centres and Máxima Medical Centre in Eindhoven.

This has resulted in the combination of more knowledge and expertise and provides patients with the opportunity to receive optimal treatment in their own district. In clinical practice the Dutch Adrenal network participates in telephone consultation by local doctors, referral of patients to one of the regional centres, and referral of patients from regional centres to the trial centres (Leiden University Medical Centre (LUMC), Academic Medical Centre (AMC) and Máxima Medical Centre (MMC). In the VU University Medical Centre (VUmc) and the University Medical Centre Groningen (UMCG) the trial has been presented to the METC. The Dutch Adrenal Network also plays an important role in determining and/or modifying the treatment policy for patients with adrenal cortical carcinoma.

The Dutch Adrenal Network strives to increase knowledge of both the pathogenesis and the prognostic factors of the disease.

In early 2005, 53 patients were treated in the Network, which reflects about 50% of the total population with adrenocortical carcinoma in the Netherlands. The goal is to increase this number, so that more patients get the best possible treatment and care.

CONCLUSION

Adrenocortical carcinoma is a rare disease with a poor prognosis. Chemotherapy can be effective in patients with metastatic disease. To improve the treatment of adrenocortical carcinoma, national and international cooperative alliances have been set up. International cooperation has resulted in a randomised trial aimed at determining a standard therapy for advanced adrenocortical carcinoma. The Dutch Adrenal Network is a national cooperation with the primary goal to give patients the best possible treatment, by bringing together knowledge and expertise, and trying to implement this regionally.

APPENDIX 1

The Dutch Adrenal Network
Radboud UMC Nijmegen: Prof. Dr. A.R.M.M. Hermus
UMCG Groningen: Prof. Dr. B.H.R. Wolffenbuttel
AMC Amsterdam: Dr. J.H. de Vries, Dr. J.W. Wilmink
LUMC Leiden: Prof. Dr. J.A. Romijn, Dr. A.J. Gelderblom
VUmc Amsterdam: Dr. M. Eekhoff

AZM Maastricht: Dr. N.C. Schaper, Dr. A.P. de Bruine
UMCU Utrecht: Dr. P.M.J. Zelissen
Erasmus MC, Rotterdam: Dr. W.W. de Herder, Dr. R.R. de Krijger
MMC Eindhoven: Dr. M.W. Dercksen

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