The long-term survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane

B Wängberg¹, A Khorram-Manesh¹, S Jansson¹, B Nilsson¹, O Nilsson², C E Jakobsson³, S Lindstedt³, A Odén⁴ and H Ahlman¹

Departments of ¹Surgery, ²Pathology and ³Clinical Chemistry, Sahlgrenska University Hospital, University of Gothenburg, 413 45 Gothenburg, Sweden
⁴Department of Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden

(Correspondence should be addressed to H Ahlman; Email: hakan.ahlman@surgery.gu.se)

Abstract

Adrenocortical carcinoma (ACC) is a rare tumour disease with sinister prognosis also after attempts to radical surgery; better prognosis is seen for low-stage tumours. Adjuvant treatment with the adrenolytic drug mitotane has been attempted, but not proven to prevent from recurrence. The drug may offer survival advantage in case of recurrence. The aim of this single-centre study (1979–2007) of 43 consecutive patients was to evaluate the long-term survival after active surgical treatment combined with monitored mitotane (to reduce side effects of the drug). The series is unique, since all patients were offered a period of mitotane as adjuvant or palliative treatment; six patients refused mitotane. Despite a high proportion of high-stage tumours (67%), the complete resection rate was high (77%). The disease-specific 5-year survival was high (64.1%); very high for patients with low-stage tumours without evident relation to mitotane levels. Patients with high-stage tumours had a clear survival advantage with mitotane levels above a threshold of 14 mg/l in serum. The hazard ratio for patients with high mitotane levels versus all patients indicates a significant effect of the drug. The results indicate that adjuvant mitotane may be the standard of care for patients with high-stage ACC after complete resection.

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumour disease with low 5-year survival (16–38%; Dackiw et al. 2001, Abiven et al. 2006, Allolio & Fassnacht 2006, Libe et al. 2007) due to frequent recurrence even after attempts to radical resection (Icard et al. 1992, Bellantone et al. 1997, Schulick & Brennan 1999). Adjuvant treatment with the adrenolytic drug mitotane (o,p'-DDD), which blocks cortisol synthesis by inhibiting 11β-hydroxylation and cholesterol side chain cleavage, has been attempted but not convincingly proven to protect from recurrence (Schteingart et al. 2005). In a recent series of patients with ACC responsiveness to mitotane indicated a survival advantage when given for recurrent disease (Gonzalez et al. 2007). The toxicity of mitotane (gastrointestinal and central nervous side effects) has been a major obstacle for its use. Van Slooten et al. (1984) introduced monitoring of serum mitotane levels in order to reduce the side effects. From retrospective studies, a therapeutic threshold of mitotane (>14 mg/l) was suggested (Haak et al. 1994, Baudin et al. 2001). Monitored mitotane treatment combined with chemotherapy, etoposide, doxorubicin and cisplatin (EDP-regimen) versus streptozotocin is currently under investigation for palliative purposes in the FIRM-ACT study (http://www.firm-act.org).

The prognosis in ACC relates to tumour stage (Icard et al. 2001, Abiven et al. 2006) and certain histopathological features, e.g. high mitotic count (>20 mitoses per 50 high-power fields; Weiss et al. 1989). According to the Mac Farlane staging (Mac Farlane 1958) modified by Sullivan et al. (1978), the low stages (I and II) represent small (<5 cm) or large (>5 cm) tumours confined to the adrenal, while high-stage
tumours show infiltrative growth or lymph node metastases (stage III) or invasion of adjacent organs, positive lymph nodes or distant metastases (stage IV). A better survival is usually seen in younger patients (Abiven et al. 2006). Secretion of cortisol and androgens is often associated with ACC (Abiven et al. 2006, Allolio & Fassnacht 2006) probably less than one-third are non-hypersecretory after careful hormonal investigations (Libe et al. 2007). The worse prognosis for cortisol-secreting ACC may relate to the morbidity of hypercortisolism and/or a different tumour biology (Berruti et al. 2005, Gonzalez et al. 2007). Using gas chromatography/mass spectrometry (GC–MS) to determine urinary steroid profiles, ACC patients seem to have a dominance of steroid intermediaries like 11-deoxycortisol and 3-β-hydroxy-5-ene steroids (Gröndal et al. 1990, Kikuchi et al. 2000).

The aim of this study was to evaluate the long-term results of an active surgical programme combined with monitored mitotane therapy in a consecutive single-centre series of patients with ACC over 28 years. The series is unique, since all patients were offered a period of mitotane treatment after primary surgery regardless of tumour stage and completeness of resection.

Patients and methods
Forty-three consecutive patients with ACC (20 males and 23 females, median age 54 years; range 20–84 years) were treated surgically at our referral centre (which serves the western region of Sweden with 1.6 million inhabitants) between 1979 and 2007 aiming at complete tumour resection. The diagnosis of ACC was in all cases confirmed by histopathological examination of resected tumours (atypical light microscopic features and immunohistochemical profiles; Weiss et al. 2004). The malignant potential was assessed by Weiss scoring. In patients with non-resectable disease, tumour-reducing procedures were attempted and repeat surgery of resectable recurrences was performed; five surgeons were active in the programme during the study period. The follow-up included tumour steroids in plasma and urine every 3 months and computed tomography (CT) every 6 months during the first 5 years; patients with no signs of recurrence were therefor controlled annually (Khorram-Manesh et al. 1998, Schteingart et al. 2005). Urinary steroid profiling has been in use at our centre since 1990 using extraction according to Schmidt et al. (1985) followed by GC–MS (Moolenaar et al. 1977). If a patient developed an aberrant steroid profile in comparison with the one after intentionally curative resection, repeat radiological exams were performed. Monitoring of mitotane levels was simultaneously initiated at our centre using a modified capillary GC technique with electron capture detector (Benecke et al. 1987). The mitotane analysis was accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC) and was performed in the same laboratory throughout the study.

The series included 33% low-stage tumours (no stage I, 14 stage II) and 67% high-stage tumours: 11 stage III (five tumours with caval ingrowth) and 18 stage IV tumours. Steroid hypersecretion was verified in 17 patients (Table 1).

Primary surgery
All 25 patients with stage II and III tumours underwent radical (R0) resection, and 8 out of 18 patients with stage IV tumours were resected for intentional cure. Concomitant resection of kidney, liver, spleen, pancreas, stomach, colon and wall of the caval vein was only performed when direct tumour extension to these organs was suspected. Ten patients with stage IV tumours underwent tumour debulking (<10% residual tumour), which included liver resection in six patients (Fig. 1).

Repeat surgery
Ten patients (six stage II, three stage III and one stage IV tumours) underwent repeat surgery for recurrence; in all

| Age – year | Median 54 | Range 20–84 |
| Sex – no. (%) | Male 20 (47%) | Female 23 (53%) |
| Tumour stage – no. (%) | Low-stage | I – (0%) | II 14 (33%) |
| High-stage | III 11a (26%) | IV 18 (41%) |
| Weiss scoreb | Median 6 | Range 4–8 |
| Tumour diameter (cm) | Median 13 | Range 6–20 |
| Functional status of tumour – no. (%) | Glucocorticoids +/− androgens 14 | Androgens 1 | Aldosterone 1 | Oestradiol 1 |

aFive with caval vein ingrowth.
bThe Weiss score ranges from 0 to 9; a score higher than 2 indicates ACC.
the patients, 16 re-operations were performed (Table 2). The median time to first recurrence was 16 months (range 3–84). Two patients with stage II or stage III tumours and first recurrence within 6–13 months have no evidence of disease 34 and 159 months after primary surgery respectively. One patient with stage II tumour died 18 months after primary surgery of cardiovascular disease.

Mitotane treatment

All the patients were offered mitotane treatment after histopathological confirmation of the diagnosis (<4 weeks after resection). The dosage of mitotane was titrated from an initial dose of 2 g/day by monitoring of serum levels every 2 weeks during the first 2–3 months and was adjusted to a defined therapeutic interval (14–20 mg/l; Van Slooten et al. 1984, Haak et al. 1994, Baudin et al. 2001). These patients were referred as the high mitotane category. Thereafter, mitotane levels were followed every 3 months or earlier on suspicion of side effects. Four patients treated prior to 1990 (when mitotane monitoring was not available) only received a low dose of the drug (1 g × 2). All the patients with mitotane were adjusted to adequate cortisol replacement. Thyroid function was controlled every 6 months.

Table 2 Repeat surgery performed and clinical outcome

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at first surgery (years)</th>
<th>Tumour stage</th>
<th>Time to first recurrence (months)</th>
<th>Tumour sites a. first b. second c. third recurrence</th>
<th>Outcome and follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>50</td>
<td>II</td>
<td>6</td>
<td>a. local + liver + lung</td>
<td>DOD (10)</td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
<td>II</td>
<td>3</td>
<td>a. local</td>
<td>DOC (18)</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>II</td>
<td>6</td>
<td>a. local + liver + kidney</td>
<td>NED (34)</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>IIIa</td>
<td>19</td>
<td>a. local + adrenal</td>
<td>DOD (38)</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>II</td>
<td>12</td>
<td>b. local + carcinosis</td>
<td>DOD (42)</td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>III</td>
<td>20</td>
<td>a. local + ICV</td>
<td>DOD (44)</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>II</td>
<td>21</td>
<td>a. spine</td>
<td>DOD (72)</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>IV</td>
<td>19</td>
<td>b. local + liver</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
<td>IIIa</td>
<td>13</td>
<td>a. lung</td>
<td>DOD (128)</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>II</td>
<td>84</td>
<td>b. adrenal</td>
<td>NED (159)</td>
</tr>
</tbody>
</table>

ICV, inferior caval vein; DOD, dead of disease; DOC, dead of other causes; NED, no evidence of disease.

*Stage III with caval ingrowth.
Mitotane treatment in an adjuvant setting was offered to all 33 patients with complete resection (Fig. 1). In patients without observed recurrence, the treatment was interrupted at 3 years prior to 1998 or at 2 years thereafter. All ten patients with resectable recurrence (Table 2) were recommended mitotane treatment during 2 years after latest recurrence or life-long treatment of patients with non-resectable disease (Fig. 1).

**Palliative treatment**

Ten patients with stage IV disease underwent tumour-reducing abdominal surgery; all received additional treatment besides mitotane, e.g. chemotherapy (doxorubicin, EDP or streptozotocin), or one received external radiotherapy for bone metastases and one chemoembolisation of the liver (doxorubicin; Fig. 1). Six of these patients died of ACC after a median observation of 8 (range 3–24) months, one of unrelated causes and three are alive with residual tumour 2–8 months after primary surgery. Of the eight patients with non-resectable recurrence, six were offered a period of chemotherapy (EDP or streptozotocin) in addition to mitotane and two had external radiotherapy of bone metastases (Fig. 1).

**Statistical analysis**

Estimated disease-specific survival and overall survival were calculated according to the Kaplan–Meier method. A Poisson model was applied to study the hazard function of death from ACC. In a Poisson regression, the variables time since surgery, high-stage tumours (III and IV), tumour size, Weiss score and high mitotane levels (> 14 mg/l) were included, and the respective hazard ratios were calculated. By use of the result of the Poisson regression, the hazard ratio for patients with high mitotane levels versus all patients was compared up to 5 years after primary surgery.

**Results**

**Compliance with mitotane treatment**

Twenty-four patients (75% high-stage tumours) were kept at mitotane levels exceeding 14 mg/l. Thirteen patients (62% high-stage tumours) did not tolerate this drug level and were kept at lower levels; five still experienced so severe side effects (nausea \( n = 5 \), central nervous symptoms \( n = 3 \) and exanthema \( n = 1 \) ) that mitotane was ceased. Six patients (50% high-stage tumours) denied mitotane due to high age or severe co-morbidity. Thus, 24 out of 37 patients (65%) had good compliance with the drug, and 8 could tolerate the drug at reduced levels (22%); 5 abandoned mitotane therapy (13%).

**Estimated survival**

The current series has a preponderance of high-stage tumours (67%), but nevertheless the complete resection rate was high (77%). Eighty-seven percentage of all the patients were treated with mitotane for 2 years or longer. The disease-specific survival at 5 years for the entire series was 64.1% (Fig. 2A), and the corresponding overall survival was 52.0% (Fig. 2C).
6 patients had high mitotane levels and stage II tumours (80.0%, estimated 5-year survival), and 18 patients had high mitotane levels and high-stage tumours (III or IV; 64.0%, estimated 5-year survival). Eight patients had low mitotane levels and stage II tumours (87.5%, estimated 5-year survival) and 11 patients had low mitotane levels and high-stage tumours (28.6%, estimated 5-year survival); the analysis includes three patients with stage II and 3 patients with high-stage tumours that never started mitotane (Fig. 2B). Neither Weiss score ($P = 0.47$) nor tumour size ($P = 0.23$) contributed significantly to the prediction of disease-specific survival in the multivariate context. Since there were no stage I ($<5$ cm) tumours in this series, the influence of tumour size was also assessed ($P = 0.23$).

### Hazard of dying from ACC

This function was studied by Poisson regression (Table 3). In this series, time since surgery did not significantly influence the hazard ratio, but this ratio was more than twofold increased for patients with high-stage tumours. High mitotane levels were associated with a significantly reduced hazard ratio ($P < 0.049$).

When the hazard ratio for death of ACC was compared over time between the patients with high mitotane levels ($>14$ mg/l) versus patients with lower dose or without mitotane, the curve strongly indicated a positive survival effect by mitotane from 8 months up to 4 years after primary surgery (Fig. 3).

#### Urinary steroid profiles

This analysis enabled biochemical detection of recurrence in five patients due to the appearance of $3\beta$-hydroxy-5-ene steroids. The finding was concomitant with positive radiological findings in three and with small miliary tumours at second look in two patients; none was cured. One female patient developed moderate secretion of androsterone without radiological signs of recurrence and negative second look; she is still disease-free 10 years later.

### Discussion

ACC is an aggressive tumour disease with clinical course that can be difficult to predict also in patients with radically resected low-stage tumours (Vassilopoulou-Sellin & Schultz 2001). Besides tumour staging and Weiss score, several molecular markers have been suggested for prognostication but not yet reached clinical practice (Schteingart et al. 2005). Intentionally curative surgery increases the 5-year survival in stage I–III disease (Kendrick et al. 2001). In two national series (Icard et al. 1992, Bellantone et al. 1997) and one large series from a US referral centre (Schulick & Brennan 1999; each comprising 113–156 patients), the proportion between low- and high-stage tumours was 1:1 and the complete resection rate varied between 60 and 81%. The 5-year survival after complete re-resection varied between 28 and 57% and was very low after incomplete re-resection.

Terzolo et al. (2007) recently addressed adjuvant mitotane treatment in a retrospective study of 177 patients with ACC (only 28% high-stage tumours) subjected to radical surgery; the study collected

### Table 3 The hazard function of death by tumour disease studied by Poisson regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$</th>
<th>S.E.M.</th>
<th>$P$ value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-1.9816</td>
<td>0.6591</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since surgery (years)</td>
<td>-0.2726</td>
<td>0.1761</td>
<td>0.1217</td>
<td>0.76</td>
<td>0.54–1.08</td>
</tr>
<tr>
<td>Stage III or IV (no=0, yes=1)</td>
<td>0.9206</td>
<td>0.6028</td>
<td>0.1267</td>
<td>2.51</td>
<td>0.77–8.18</td>
</tr>
<tr>
<td>Mitotane &gt; 14</td>
<td>-1.4002</td>
<td>0.7124</td>
<td>0.0494</td>
<td>0.25</td>
<td>0.06–1.00</td>
</tr>
<tr>
<td>Mitotane &gt; 14×time</td>
<td>0.2536</td>
<td>0.1920</td>
<td>0.1867</td>
<td>1.29</td>
<td>0.88–1.88</td>
</tr>
</tbody>
</table>

**Figure 3** The hazard ratio for death of tumour disease (red curve) over time since surgery. The two black curves represent the 95% confidence interval. The hazard ratio compares patients with high mitotane levels ($>14$ mg/l) versus all other patients (including patients without mitotane). Stage was included in the analysis. The upper limit of the confidence interval was $<1$ in the interval 8 months to 4 years (the blue line $y=1$ corresponds to no effect at all).
patients from 8 centres in Italy and 47 centres in Germany between 1985 and 2005. Forty-seven Italian patients were treated with mitotane without monitoring of drug levels and compared with 55 Italian and 75 German patients with no adjuvant treatment. There was a bias in the study with more elderly and low-stage patients in the German series versus the mitotane-treated group. The median recurrence-free survival was longer (42 months) in the mitotane group versus each of the two control groups (10 and 25 months respectively). The overall 5-year survival was almost 70% for the mitotane group versus 50–55% for controls indicating therapeutic benefits of mitotane in an adjuvant setting. In the large French retrospective study, mitotane treatment also seemed to offer survival advantage for patients with metastatic or residual ACC (Icard et al. 2001).

Our consecutive series using a uniform surgical programme during a long-time period together with monitored mitotane treatment clearly indicates the therapeutic benefits of the drug. The disease-specific survival and overall 5-year survival were high (64.1 and 52.0% respectively) despite a preponderance of high-stage tumours (67%); ten patients with non-radical surgical procedures were included in the series. To date, 15 out of the 43 patients are recurrence-free (nine high-stage tumours). In ten patients undergoing repeat surgery due to tumour recurrence, a median survival of 43 months was achieved and two have no evidence of disease. These results favour an active surgical attitude in patients with resectable recurrence as previously indicated by other studies (Bellantone et al. 1999, Schulick & Brennan 1999, Gonzalez et al. 2007). Debunking procedures of non-resectable stage IV tumours were not associated with major complications but can be questioned since only few patients lived longer than 1 year despite mitotane in combination with several other treatment modalities. In a recent study of 186 patients with ACC (60% low-stage tumours) treated at the M.D. Anderson Cancer Centre over 15 years, only 23 had their primary surgery at this hospital (Gonzalez et al. 2007). The median overall survival was 37 months (33%, estimated 5-year survival). One hundred and seventy-four complete resections were performed and 38 patients remained tumour free. Since this series is mainly based on recurrent ACC, the use of mitotane in this setting was studied; out of 69 evaluable patients with recurrent ACC, 19% showed stable, or responsive, disease to mitotane treatment, which related to more favourable prognosis. Patients with incomplete resection were treated with chemotherapy, and a minority of the recurrent cases received mitotane combined with chemotherapy. Based on these results, the authors recommend mitotane to most patients with recurrent ACC and even suggest preoperative treatment to patients considered for re-resection.

The urinary steroid profile might be an instrument for early detection of recurrence. However, in this series five cases with ‘early’ appearance of steroid intermediaries proved to be concomitant with non-resectable tumour; one case had falsely elevated androsterone levels. Taken together, these results limit the clinical usefulness of urinary steroid profiles in this aggressive disease. The individual steroid secretory pattern can vary largely due to age, sex, menstrual cycle and medication, which makes a numerical analysis of key steroids difficult in the absence of a large reference material.

In the present series, the 5-year survival was very high for patients with stage II tumours without evident relation to mitotane levels (80.0–87.5%). The estimated 5-year survival for patients with high-stage tumours was markedly better (64.0%) for those with high mitotane levels than for those with low levels (28.6%). Even though side effects can be reduced by monitoring of mitotane, 13% of the patients in this study abandoned mitotane treatment even after dose reduction. Several studies (Scheingart et al. 1982, Luton et al. 1990, Dickstein et al. 1999, Terzolo et al. 2007) indicate that early administration of mitotane after radical surgery may improve disease-free and overall survival, but the critical prospective two-arm trial is still lacking, e.g. mitotane therapy for 2 years and follow-up for another 3 years with time to first recurrence as primary outcome. The present retrospective series indicates a survival advantage by mitotane for patients with high-stage tumours.

When the hazard of dying from ACC was studied, high mitotane levels were associated with a significantly reduced risk. When the hazard ratios for patients with high mitotane levels versus all other patients were compared over time after primary surgery, a protective effect of the drug was indicated from 8 months up to 4 years. The delayed onset of this effect may relate to the time it takes to establish therapeutic levels of the drug. The temporary effect may reflect that patients with high-stage tumour/residual tumour died within this period, and that some patients with adjuvant mitotane for 2 years recurred and died after cessation of the drug (Fig. 1).

We conclude from this series with predominantly high-stage tumours that favourable long-term survival was reached when active interventions were combined with mitotane treatment; monitoring of drug levels was helpful to reduce side effects, and the
compliance with mitotane treatment was relatively high. For patients with low-stage tumours, high survival was reached irrespective of mitotane levels. On the other hand, patients with high-stage tumours had a significant survival advantage of high mitotane levels. The results from the Italian–German adjuvant mitotane study (Terzolo et al. 2007), and the present series suggests that adjuvant mitotane may well be the standard of care for high-stage ACC after complete resection. In patients with residual tumour or non-resectable recurrence, mitotane must be combined with chemotherapy. Ongoing randomised multi-centre studies will hopefully offer guidance in the choice of best chemotherapy for palliative purposes in addition to mitotane.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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