MITOTANE FOR THE MANAGEMENT OF ADRENOCORTICAL CARCINOMA

Date Developed: November 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Adrenocortical carcinomas (ACC) are rare, occurring at a rate of 0.72 per 1 million. ACC are typically diagnosed in the advanced stages, and associated with a poor prognosis. Overall 5-year survival rates are typically 38 to 46%. Prognosis is affected by stage of disease, completeness of resection, and pathologic grade of the tumour. The tumour grade is determined by the mitotic rate, with >20 mitoses per 50 high power fields defining high-grade disease, and ≤20 mitoses per high power field designated as low-grade. Information on the staging definitions for ACC as defined by the American Joint Committee on Cancer Staging can be found in Appendix A.

ACC are often designated “functioning” or “nonfunctioning” tumours. Functioning tumours can produce symptoms associated with the over-production of hormones, such as cortisol, androgens, and mineralocorticoids. Therapeutic management directed at controlling symptoms related to excess hormone production is extremely important in the treatment of patients with functional ACC. Treatment of ACC typically consist of radical open surgical excision in patients with resectable disease. Several drugs have been tested in the adjuvant setting, with varying degrees of efficacy. For patients with advanced unresectable ACC, there are limited options for treatment.

Mitotane, a hormone antagonist, is commonly used in the management of adrenocortical carcinoma. Mitotane’s exact mechanism of action is unknown although data suggest that it modifies the peripheral metabolism of steroids and has a directly suppressive effect on the adrenal cortex. Mitotane may be effective in the management of ACC by controlling symptoms and possibly slowing tumour growth. The purpose of this guideline is to provide evidence-based recommendations on the use of mitotane in patients with ACC and to define which patients are acceptable candidates for treatment with this agent.

GUIDELINE QUESTIONS

- Does adjuvant mitotane delay recurrence or prolong survival in patients with resectable adrenocortical carcinoma? If so, what is the appropriate dosing regimen for mitotane in this setting?
- Does mitotane, in combination with other anti-tumour agents, prolong survival in patients with advanced unresectable adrenocortical carcinoma? If so, which combination is most effective, and at what dose, in this setting?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU handbook.

SEARCH STRATEGY

The PubMed and Medline databases were searched (1965 through 2013 July 16) for relevant publications using the following search terms: (mitotane or lysodren) and (adrenocortical carcinoma or [adrenal gland and neoplasm]). Results were limited to randomized controlled trials, phase II-III clinical trials, meta-analyses, and guidelines. In addition, the National Guidelines Clearinghouse database was searched (2008 through 2013 July 16) for additional guidelines and the American Society of Clinical Oncology.
(ASCO) meeting abstracts database was searched (2011 through 2013 July 16) for relevant abstracts. A total of eleven and fifteen citations were returned from PubMed and Medline, respectively; seven were relevant and therefore included in the literature review. One ASCO abstract was included as well. No additional guidelines were identified in the National Guidelines Clearinghouse database; however, protocols for the use of mitotane were retrieved from the BC Cancer Agency website. Evidence is summarized in the table in Appendix B.

TARGET POPULATION

The recommendations in this guideline apply to patients diagnosed with adrenocortical carcinoma.

RECOMMENDATIONS

1. Patients with resectable adrenocortical carcinoma. Adjuvant mitotane has been shown to delay or prevent disease recurrence in patients with resected adrenocortical carcinomas (ACC). Adjuvant mitotane should be considered for use in this setting.
   - Mitotane is administered orally, beginning with a dose of 2-6 g per day, in divided doses given q 6-8 hours. The dose should then increase by 1 g per day, once every 1-2 weeks, to a maximum tolerated dose. The usual dose is 8-10 g per day, in divided doses, but the maximum tolerated dose may vary. The maximum dose should not exceed 19 g per day. 7
   - Patients with potential residual disease (R1 or Rx resection) and/or Ki67 more than 10% should be offered adjuvant mitotane.

2. Patients with advanced unresectable adrenocortical carcinoma. Mitotane-based combination therapy has been shown to slow disease progression in patients with advanced unresectable adrenocortical carcinoma. Therefore, mitotane-based combination therapy is recommended for use in this setting.
   - Combination therapy should consist of continuous oral mitotane titrated to a blood level of 14-20 mg/L, followed 1 week later by chemotherapy consistent with the recommendations from the FIRM-ACT study. Doxorubicin (40 mg/m^2 IV on day 1), etoposide (100 mg/m^2 IV on days 2, 3, and 4), and cisplatin (40 mg/m^2 IV on days 3 and 4), given in 4-week cycles or streptozocin (1 g on days 1 to 5 in cycle 1; 2 g on day 1 in subsequent cycles) every 3 weeks are both options that can be considered for patients appropriate for treatment with chemotherapy. 8

DISCUSSION

A summary of the key evidence used to inform the recommendations is provided below. Full evidence tables on the use of mitotane in adrenocortical carcinoma can be found in Appendix B.

Resectable Adrenocortical Carcinoma

Primary therapy for resectable adrenocortical carcinoma (ACC) is radical surgical resection. 3 Prognosis following surgery depends on the completeness of surgical resection. 3,4 However, mitotane may control tumour growth in patients with residual disease and reduce the risk of recurrence in those with no residual disease following resection. A retrospective analysis of data from patients who had undergone radical resection followed by either mitotane (1-5 g per day; n=47) or no adjuvant treatment (n=75) showed that the rate of recurrence was lower in patients who received mitotane (48.9% vs. 73.3%) and median overall survival was significantly longer (110 months vs. 67 months). 9 Another retrospective analysis of patients with ACC treated with surgical resection found that the risk of recurrence was higher among those who
did not receive adjuvant mitotane (HR 1.95, 95% CI 1.06-3.59; p=.03). Mitotane has been shown to be associated with prolonged survival in children with ACC.\(^\text{11}\)

No phase III randomized control trials, comparing mitotane therapy with no therapy in patients with resectable ACC were identified from the literature search. However, an environmental scan of clinical practice guidelines on ACC revealed that adjuvant mitotane is supported by the British Columbia Cancer Agency,\(^\text{7}\) the European Society for Medical Oncology,\(^\text{12}\) by the European Association of Urology,\(^\text{13}\) and in International Consensus Guidelines.\(^\text{14,15}\) Patients with non-localized ACC, any residual disease, or >10% Ki-67 proliferation marker should be treated with mitotane, according to the guideline.\(^\text{15}\)

Based on evidence from retrospective studies and clinical practice guidelines, it recommended that patients with resectable adrenocortical carcinoma be treated with adjuvant mitotane; oral mitotane should start at 2 to 6 g per day in total, in divided doses given every 6 to 8 hours. The dose should then increase by 1 g per day, once every 1 to 2 weeks, to a maximum tolerated dose. The usual dose is 8 to 10 g per day, in divided doses, but the maximum tolerated dose may vary and should not exceed 19 g per day.\(^\text{7}\) Patients with potential residual disease (R1 or Rx resection) and/or Ki67 more than 10% should be offered adjuvant mitotane.\(^\text{12}\)

### Advanced Unresectable Adrenocortical Carcinoma

Advanced unresectable ACC carries a poorer prognosis than localized ACC.\(^\text{5,15}\) The 5-year overall survival rate in patients with stage IV ACC is typically less than 20%.\(^\text{2,3}\) Chemotherapy alone has shown little efficacy.\(^\text{13,16,17}\) Mitotane, however, has shown more promising results. Two separate phase II trials by Berruti, et al. combined etoposide (100 mg/m\(^2\) days 5-7), doxorubicin (20 mg/m\(^2\) days 1 and 8) and cisplatin (40 mg/m\(^2\) days 2 and 9) with mitotane (1-4 g per day) in patients with advanced unresectable ACC (n=100 in total); the overall response rate ranged from 49% to 54% with a complete response in approximately 7% of patients and a partial response in 42% to 46% of patients.\(^\text{18,19}\) Median overall survival in the larger of the two studies was 28.5 months.\(^\text{18}\)

The first and only phase III randomized controlled trial to date on the use of mitotane in patients with ACC was published in 2012; Fassnacht, et al. (FIRM-ACT Study Group) compared mitotane plus etoposide (100 mg/m\(^2\) days 2-4), doxorubicin (40 mg/m\(^2\) day 1) and cisplatin (40 mg/m\(^2\) days 3 and 4) every four weeks (M-EDP) with mitotane plus streptozotocin (1 g days 1-5 in cycle 1; 2 g on day 1 in subsequent cycles) every 3 weeks (M-Sz) in patients with advanced ACC (n=304). Mitotane dosing was titrated to a blood level of 14-20 mg/L. As first-line therapy, the response rate was higher (23.2% vs. 9.2%; p<.001) and the median duration of progression-free survival was longer (5.0 months vs. 2.1 months; hazard ratio 0.55, 95% CI 0.43-0.69; p<.001) in patients treated with M-EDP; however, there was no significant in overall survival (14.8 months vs. 12.0 months; hazard ratio 0.79, 95% CI 0.61-1.02; p=.07) between groups. As second-line therapy, the median duration of progression-free survival was also longer in patients treated with M-EDP (5.6 months vs. 2.2 months).\(^\text{8}\)

Based on phase III data, patients with advanced unresectable adrenocortical carcinoma who are appropriate candidates for palliative systemic chemotherapy can be offered treatment with mitotane-based combination therapy consisting of continuous oral mitotane titrated to a blood level of 14-20 mg/L, followed 1 week later by doxorubicin (40 mg/m\(^2\) IV on day 1), etoposide (100 mg/m\(^2\) IV on days 2-4), and cisplatin (40 mg/m\(^2\) IV on days 3 and 4), given in 4-week cycles.
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>adrenocortical carcinoma</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>DFS</td>
<td>disease-free survival</td>
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<tr>
<td>OS</td>
<td>overall survival</td>
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<tr>
<td>PFS</td>
<td>progression-free survival</td>
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</table>

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


APPENDIX A: AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM (7th EDITION, 2010) FOR ADRENOCORTICAL CARCINOMA

Primary Tumor (T)
TX: Primary tumor cannot be assessed.
T0: No evidence of primary tumor.
T1: Tumor ≤5 cm in greatest dimension, no extra-adrenal invasion.
T2: Tumor >5 cm, no-extra adrenal invasion.
T3: Tumor of any size with local invasion, but not invading adjacent organs (kidney, diaphragm, great vessels, pancreas, spleen, liver).
T4: Tumor of any size with invasion of adjacent organs (kidney, diaphragm, great vessels, pancreas, spleen, liver).

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be assessed.
N0: No regional lymph node metastasis.
N1: Regional lymph node metastasis.

Distant Metastasis (M)
M0: No distant metastasis.
M1: Distant metastasis.

Anatomic Staging for Adrenocortical Carcinoma
Stage I: T1, N0, M0
Stage II: T2, N0, M0
Stage III: T1-3, N0-1, M0
Stage IV: T3-4, N0-1, M0 and any T, any N, M1
APPENDIX B: CLINICAL STUDIES USING MITOTANE IN PATIENTS WITH ADRENOCORTICAL CARCINOMA

### Table 1: Clinical data

<table>
<thead>
<tr>
<th>Author (trial)</th>
<th>Design</th>
<th>Treatments</th>
<th>Patients (n)</th>
<th>Response</th>
<th>Survival</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassnacht 2012</td>
<td>phase III RCT</td>
<td>1. Mitotane titrated to 14-20 mg/L + etoposide 100 mg/m² day2-4, doxorubicin 40 mg/m² day1, cisplatin 40 mg/m² day3, 4 every 4 weeks (EDP-M) 2. Mitotane titrated to 14-20 mg/L + streptozocin 1 g on days 1-5 in cycle 1; 2 g on day 1 in subsequent cycles) every 3 weeks (Sz-M)</td>
<td>advanced ACC who were treatment-naive or who failed 1st line (n=304)</td>
<td>23.2% EDP-M 9.2% Sz-M</td>
<td>PFS (med) 5.0 mos EDP-M vs. 2.1 mos Sz-M OS (med) 14.8 mos EDP-M vs. 12.0 mos Sz-M</td>
<td>EDP-M (any 58.1%) bone marrow toxicity (11.5%) cardiovascular/thromboembolic events (6.8%) infection (6.8%) Sz-M (any 41.6%) gastrointestinal (8.1%) fatigue or general health deterioration (4.7%) impaired liver function (4.7%)</td>
</tr>
<tr>
<td>Berruti 2005</td>
<td>prospective phase II study</td>
<td>Mitotane 1-4 g per day Etoposide 100mg/m² days 5-7 Doxorubicin 20mg/m² days 1, 8 Cisplatin 40mg/m² days 2, 9 q 4 weeks x 6 cycles</td>
<td>advanced ACC, non-amenable to radical surgery (n=72)</td>
<td>48.6% overall 6.7% complete (n=5) 41.7% partial (n=30)</td>
<td>TTP (med) 9.1 mos OS (med) 28.5 mos</td>
<td>Hematologic, gastrointestinal or neurologic toxicities One toxic death due to septic shock caused by prolonged neutropenia</td>
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<tr>
<td>Berruti 1998</td>
<td>phase II trial</td>
<td>Mitotane 1-4g per day Etoposide 100mg/m² days 5-7 Doxorubicin 20mg/m² days 1, 8 Cisplatin 40mg/m² days 2, 9 q 4 weeks</td>
<td>advanced, inoperable ACC (n=28)</td>
<td>53.6% overall response 7.1% complete (n=2) 46.4% partial (n=13) complete hormone response in 9/16 pts</td>
<td>TTP (med) in responsive patients 24.4 mos</td>
<td>increased serum levels of cholesterol and triglycerides</td>
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<td>Bukowski 1993</td>
<td>phase II trial</td>
<td>Poor risk: 75mg/m² cisplatin per 3 weeks + 1 g mitotane 4/day Good risk: 100 mg/m² cisplatin per 3 weeks + 1 g mitotane 4/day</td>
<td>metastatic or residual ACC (n=37)</td>
<td>30% (11/37) 2.7% complete (n=1) 27.0% partial (n=10)</td>
<td>OS (med): 11.8 mos</td>
<td>47% pt had ≥gr 3 toxicity Most common side effects were gastrointestinal, renal, and neurologic.</td>
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<tr>
<td>Khan 2000</td>
<td>phase II trial</td>
<td>1. IV Streptozocin 1 g per day (5 days) or 2 g per 3 weeks 2. oral mitotane 1-4 g per day everyday</td>
<td>ACC (n=40)</td>
<td>response 36.4% (overall)</td>
<td>OS (mean): 64±9mos (med 47 mos, range 2-243) OS (2-yr): 70% OS (5-yr): 32.5% OS 910-yr): 20%</td>
<td>nausea (n=20) anorexia (n=4) vomiting (n=4) vertigo (n=7) lethargy (n=6) polyneuropathy (n=2) tiredness (n=12)</td>
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<tr>
<td>Advani 2008</td>
<td>Clinico-pathological</td>
<td>1. Mitotane treatment (n=9) 2. Combination chemo (n=3)</td>
<td>ACC (n=11)</td>
<td>22% (2/9 pts) (reduction in tumour bulk) 4 pts alive at last f/u (mean 3402 d) 7 pts died (med survival 579 d)</td>
<td>gastrointestinal disturbance, dizziness, fixed drug eruption with gynaecomastia, drug-induced hepatitis</td>
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<tr>
<td>Author (trial)</td>
<td>Design</td>
<td>Treatments</td>
<td>Patients (n)</td>
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<tr>
<td>Terzolo 2007</td>
<td>retrospective</td>
<td>grade 1: mitotane (n=47)</td>
<td>ACC with prior radical surgery (n=177)</td>
<td>n/a</td>
<td>recurrence</td>
<td>GI events (15%), Neurologic (20%)</td>
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<tr>
<td></td>
<td>analysis</td>
<td>3-5g/d (n=20)</td>
<td></td>
<td></td>
<td>Gr1: 23 pt (48.9%)</td>
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<td></td>
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<td>1-3g/d (n=27)</td>
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<td>Gr2: 50 pt (90.9%)</td>
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<td></td>
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<td>grade 2: control (n=55)</td>
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<td>Gr3: 55 pt (73.3%)</td>
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<td></td>
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<td>grade 3: control (n=75)</td>
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<td>OS(med); Gr1: 110 mo</td>
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<td>Gr2: 52 mo</td>
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<td>Gr3: 67 mo</td>
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<td>ACC deaths: 73/177</td>
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<td>Baudin 2001</td>
<td>prospective</td>
<td>mitotane 6-12 mg per d</td>
<td>ACC (n=13)</td>
<td>objective response in 4 pt (1 complete) and lasted 10-48 mos</td>
<td>NR</td>
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<tr>
<td></td>
<td>phase I-II</td>
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<td>responses observed in 1 pt w/ &gt;14 mg/L mitotane</td>
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<tr>
<td>Haak 1994</td>
<td>retrospective</td>
<td>Gr2: Low dose &lt;14mg/L</td>
<td>ACC (n=62)</td>
<td>Gr2: 0% (0/32)</td>
<td>Gr2: max 12mos</td>
<td>anorexia, nausea, vomiting, diarrhoea and CNS toxicity</td>
</tr>
<tr>
<td></td>
<td>analysis</td>
<td>Gr3: High dose ≥ 14mg/L</td>
<td></td>
<td>Gr3: 20% (6/30); 3 complete</td>
<td>Gr3: mean 61mos</td>
<td>Tx discontinuation: 10 pts</td>
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<td></td>
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<td>OS(med); Gr1: 110 mo</td>
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<td>Gr2: 52 mo</td>
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<td>Gr3: 67 mo</td>
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</table>

**Table 2: Guidelines related to treating adrenocortical carcinoma**

<table>
<thead>
<tr>
<th>Guideline developer</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>ESMO 2012</td>
<td>Mitotane has been the reference drug for the management of ACC for decades. Adjuvant mitotane can delay and possibly prevent a recurrence of disease. Patients with potential residual disease (R1 or Rx resection) and/or Ki67 more than 10%, should be offered adjuvant mitotane. Mitotane dosing should be guided by plasma measurements, aiming at a concentration between 14 and 20 mg/ml. Adjuvant mitotane should be administered for at least 2 years.</td>
</tr>
<tr>
<td>European Association Urology 2011</td>
<td>Mitotane only approved drug for ACC. Mitotane target blood level in 14-20mg/L. For the first three months, regulated every 2-3 weeks, After reaching plateau interval extended to 4-6 weeks. Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic drug. The tumour response rate is 25-35% (Level of evidence: 2a). It remains to be proven whether chemotherapy prolongs survival.</td>
</tr>
<tr>
<td>BCCA Protocol Summary 2012</td>
<td>Starting dose of mitotane is 2g/d in 4 divided doses; then escalate by 1g/d once every 1-2 weeks to maximum tolerated dose. Mitotane causes potentially permanent hypoadrenalism. Patients must take cortisone acetate and fludrocortisone acetate even post-mitotane treatment.</td>
</tr>
<tr>
<td>Schteingart et al. 2005</td>
<td>Adjuvant mitotane may not improve disease-free and overall survival in ACC, but there are reports indicating that early administration of mitotane after surgery may improve overall survival. Mitotane may lead to tumor regression in some cases of stage III/IV disease.</td>
</tr>
</tbody>
</table>

*Title: Management of patients with adrenal cancer: recommendations of an international consensus conference*