High-dose mitotane strategy in adrenocortical carcinoma: prospective analysis of plasma mitotane measurement during the first 3 months of follow-up

Sophie Maculére-Denost1,2, Sophie Leboulleux1,2, Isabelle Borget5, Angelo Paci1,2, Jacques Young2,3,4,6, Abir Al Ghuzlan7, Desiree Deandreis1,2, Laurence Drouard1,2, Antoine Tabarin8, Philippe Chanson2,3,4,6, Martin Schlumberger1,2,3 and Eric Baudin1,2,4

1Department of Nuclear Medicine and Endocrine Tumors, Institut Gustave Roussy, Univ. Paris Sud, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France, 2Faculté de médecine Paris-Sud, UMR-S693, Univ Paris-Sud, Le Kremlin-Bicêtre, France, 3APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France, 4Institut National de la Santé et de la Recherche Médicale U693, Le Kremlin-Bicêtre, France, 5Department of Epidemiology, Institut Gustave Roussy, Villejuif, France, 6Department of Endocrinology, Le Kremlin Bicêtre F-94276, France, 7Department of Pathology, Institut Gustave Roussy, Villejuif, France and 8Department of Endocrinology, Haut-Levêque Hospital, Univ. Bordeaux, Avenue de Magellan, 33604 Pessac Cedex, France

(Correspondence should be addressed to E Baudin at Department of Nuclear Medicine and Endocrine Tumors, Institut Gustave Roussy, Univ. Paris Sud; Email: baudin@igr.fr)

Abstract

Background: The benefit-to-risk ratio of a high-dose strategy at the initiation of mitotane treatment of adrenocortical carcinoma (ACC) remains unknown.

Methods: To evaluate the performance of a high-dose strategy, defined as the highest tolerated dose administered within 2 weeks and maintenance therapy over 4 weeks, we conducted a single-center, prospective study with two main objectives: to evaluate the percentage of patients who achieve a plasma mitotane level above 14 mg/l and to evaluate the tolerance of mitotane within the first 3 months of treatment. Plasma mitotane levels were measured monthly using HPLC.

Results: Twenty-two patients with ACC were prospectively enrolled. The high-dose mitotane strategy (4 g/day or more in all patients, with a median of 6 g/day within 2 weeks) enabled to reach the therapeutic threshold of 14 mg/l at 1, 2, or 3 months in 6/22 patients (27%), 7/22 patients (32%), and 7/22 patients (32%) respectively. In total, a therapeutic plasma mitotane level was reached in 14 out of 22 patients (63.6%) during the first 3 months in ten patients, and after 3 months in four patients. Grade 3–4 neurological or hematological toxicities were observed in three patients (13.6%).

Conclusion: Employing a high-dose strategy at the time of mitotane initiation enabled therapeutic plasma levels of mitotane to be reached within 1 month in 27% of the total group of patients. If this strategy is adopted, we suggest that mitotane dose is readjusted according to plasma mitotane levels at 1 or/and 2 months and patient tolerance.

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive solid tumor characterized by a 5-year survival rate of below 15% for metastatic disease (1–4). Mitotane therapy continues to be a cornerstone of ACC treatment, as outlined by a recent consensus on adjuvant ACC therapy (5). The objective response rate for mitotane has been reported in prospective or retrospective studies as between 10 and 33% (6–12), and it has been suggested that mitotane has a prognostic impact for patients with metastatic ACC (9, 13–16). Mitotane is a compound derived from the insecticide dichlorodiphenyldichloroethane and has been used to treat adrenal cancer since the late 1950s. It has potent adrenotoxic effects and is able to block cortisol synthesis by inhibiting 11β-hydroxylation and cholesterol side-chain cleavage (17, 18). In 1994, Haak et al. (9) suggested that a plasma mitotane level above 14 mg/l was associated with a higher response rate and prolonged survival. Our own group has also been able to prospectively confirm these results in a separate study (11). It is now standard in most European teams to monitor the plasma mitotane level in ACC patients, with the aim of achieving a so-called ‘therapeutic plasma mitotane level’ of above 14 mg/l. However, there are several factors that must be considered in mitotane therapy. To begin with, the therapeutic window for mitotane plasma concentrations is relatively narrow. As noted earlier, a plasma mitotane concentration above 14 mg/l elicits a higher rate of objective response; however, if the plasma mitotane level rises above 20 mg/l, a higher rate of neurological adverse events is also reported (9, 11, 19). In addition, a significant
number of patients fail to reach therapeutic plasma mitotane levels at all, for reasons not yet known (9, 11, 15, 16). Finally, the long lag time from treatment start to peak levels is troublesome for advanced ACC (11, 20). Indeed, in two earlier studies, it took a median interval of 3-5 months before therapeutic levels were obtained (11, 21).

Research is ongoing to improve the management and understanding of mitotane, including studies on its molecular targets, metabolism pathways, and the galenic form of the drug (22, 23). In 2006, we proposed a high-dose mitotane strategy aimed at shortening the time required to reach the therapeutic plasma level (24). We hoped that such a strategy would help, at least partially, to overcome the poor bioavailability and lipophilic properties of the drug (16, 25). In a preliminary study, all three ACC patients who were given 3–9 g/day of mitotane reached therapeutic plasma mitotane levels by 6 weeks, with a manageable safety profile (24).

In order to confirm the benefit of this high-dose strategy, we expanded this single-center, prospective study with two main objectives: to evaluate the percentage of patients who reached a plasma mitotane level above 14 mg/l during the first 3 months of treatment (benefit) and to evaluate the unwanted effects of this high-dose mitotane strategy (risk).

Subjects and methods
All patients at the Institute of Gustave Roussy (IGR) who were started on high-dose mitotane therapy for treatment of ACC between 2005 and 2009 were enrolled in this prospective study. Patients were included in the study if their first-line high-dose mitotane treatment was initiated and followed at IGR until progression and if a review of the ACC diagnosis including the assessment of Weiss criteria was carried out. Patients were excluded if they were participating in other pharmacokinetics studies such as the PK-Lysodren trial (ClinicalTrials.gov identifier: NCT00094497) whose main goal was to study the relationship between Lysodren dose and mitotane plasma concentrations stratified for one of two pre-defined high-dose or low-dose regimens), or if they underwent concomitant treatment with chemotherapy or locoregional therapy during the study.

The definition of functional tumors was based on an increase in cortisol (assessed by measuring plasma and urinary excretion of cortisol), and/or androgen (assessed by measuring plasma testosterone, androstenedione, and DHEA sulfate), and/or estrogen (assessed by measuring 17β-estradiol) levels. Plasma 17-hydroxyprogesterone and 11-deoxycortisol levels were also measured in all patients and aldosterone and 11-deoxycorticosterone levels were measured to assess mineralocorticoid function. Staging at the diagnosis was based on imaging studies and findings at surgery and were classified according to the ENSAT classification (26). Mitotane therapy was given in an adjuvant setting in 13 patients (59%) and in a palliative setting in nine patients (41%).

Study protocol
All patients were hospitalized during the first week of therapy and had signed an informed consent form. Mitotane formulation was administered orally (Lysodren, 500 mg tablets, HRA-Pharma, Paris, France) three times daily with a meal containing fat. Mitotane starting dose was 1.5 g/day and was rapidly increased by 1.5 g/day until the highest dose was reached within the first 2 weeks (maximal daily dose 9 g/day). Clinical tolerance (especially digestive tolerance) was used to guide dose adjustment during these first 2 weeks of treatment. The aim after 2 weeks was to maintain the highest tolerated dose over at least 4 weeks. To mitigate side effects, antiemetics and or loperamide were considered on a case-by-case basis. Note, this high-dose strategy remained within the standard range of routine prescription of mitotane in our center for years (12). This strategy of prescription slightly differs with the European Summary of Product Characteristics (SPC) recommendation, available since 2004, which suggests that dosage should remain below or equal to 6 g/day. However, this strategy is in accordance with US SPC, which recommend a starting dose of 6 g/day, increasing up to 9 or 10 g/day if tolerated. Substitutive adrenal therapy, i.e. hydrocortisone 30–60 mg/day, was given immediately to all patients and fludrocortisone acetate (25–50 µg/day) was given within the first 2 weeks of therapy. Substitutive therapy was given alongside a normal salt diet and patient education by the referring physician.

Drug monitoring and toxicity evaluation
Each patient attended follow-up visits at the IGR every monthly, which included a complete clinical evaluation and routine biochemical tests. Plasma mitotane levels were measured every 4 weeks or if severe adverse effects developed. All treatments received before the initiation of mitotane were recorded. Mitotane therapy was managed by the physician and guided by clinical tolerance, biochemical test results, and plasma mitotane concentration. Mitotane-related toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria, version 3.0. In the event of grade 1–2 toxicity, the patients were allowed to reduce the daily dose by 1.5 g/day after 6 weeks. Before 6 weeks, patients were encouraged to maintain the highest dose as long as possible. In the event of unacceptable toxicity (grade 3–4), the treatment was temporarily discontinued until recovery to grade 1 and then a lower daily dose (reduced by 1.5 g/day) was
resumed. When plasma concentrations > 30 mg/l were reached, mitotane treatment was temporarily interrupted for 7 days or more depending on the presence and severity of adverse effects and then resumed at a lower dose.

Every 3 months, patients underwent hormonal and morphologic evaluation, including a computed tomography scan and FDG-PET. Tumor recurrences and responses are not described in this paper.

Plasma mitotane measurements

Plasma mitotane level was measured in the morning on an empty stomach and 12 h after the previous dose every month for the first 3 months. Mitotane measurements were performed using an HPLC method at IGR before 2008 (11) and then by PAREXEL ($r=0.98$ between the two methods, as assessed in 45 consecutive patients in 2007) after 2008. Intra-assay coefficients of variation were 20% at low values and 15% at high values. We defined a therapeutic plasma mitotane range of between 14 and 20 mg/l, a pretoxic mitotane level of between 20 and 30 mg/l, and a toxic mitotane level when concentrations exceed 30 mg/l.

Statistical analysis

Early therapeutic plasma mitotane level was defined as above: 14 mg/l at 1 month after the initiation of mitotane therapy. A correlation was sought between several parameters and achievement of early therapeutic plasma mitotane level. The following parameters were analyzed: age (median threshold 59 years), body mass index (BMI; median threshold 25 kg/m²), tumor weight and size (median threshold 600 g and 14 cm), hormone secretion (cortisol or androgen, yes or no), ENSAT Staging (stage II vs III–IV), clinical setting (adjuvant or palliative), and the mitotane dose at 2 weeks (above the median threshold 6 g/day, yes or no). The results are reported as odds ratios. A correlation was also sought between the total cumulative mitotane dose and the plasma mitotane level, using the Pearson correlation coefficient (significance was set at 5%). Categorical data was evaluated using $\chi^2$ and continued variables were compared using Student’s $t$-test. All analyses were performed using SAS software, version 9.1 (Cary, NC, USA). A P value <0.1 was considered significant at univariate analysis.

Results

Patients

Forty-seven ACC patients were referred to our institution and were treated with adjuvant or palliative mitotane. Eighteen patients were excluded because the high-dose mitotane strategy was either not started or not followed at IGR. Two patients were excluded because additional therapies were administered during the first 3 months. Five patients were excluded because they were enrolled in the PK Lysodren protocol.

Twenty-two consecutive ACC patients entered the study (eight males and 14 females; median age, 59 years; range 25–73 years; Table 1). All patients underwent surgery, including 12 patients (54%) who underwent nephrectomy. Before surgery, 15 tumors (68%) were functioning and eight patients (36%) were graded 1 according to the WHO performance status. The median time between initial surgery and the initiation of mitotane therapy was 3.5 months (range: 7 days to 3 years). The median time between the initiation of mitotane therapy and the initiation of another therapeutic modality was 6 months (3–31 months). At 6, 9, and 12 months, 12, 8, and 6 patients, respectively, were still receiving mitotane as a single therapy. According to the ENSAT classification, disease stages at the diagnosis were II, III, and IV in 27, 50, and 23% of patients respectively.

Mitotane dose and plasma mitotane levels

Among the 22 patients, three patients (14%) tolerated a maximum daily mitotane dose of 9 g, four patients (18%) tolerated a maximum daily mitotane dose of 7.5 g, six patients (27%) tolerated a maximum daily mitotane dose of 6 g, eight patients (36%) tolerated a maximum daily mitotane dose of 4.5 g, and one patient (5%) tolerated a maximum daily mitotane dose of 4 g. The median maximum daily dose administered within the first 2 weeks was 6 g/day (range: 4–9 g/day). The highest starting doses of 7.5–9 g/day achieved in seven

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics.</th>
<th>n (%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
patients were maintained over a median time of only 4 days (range: 1–45 days) while the 4–6 g starting daily doses achieved in 15 patients were maintained over a median time of 25 days (range: 2–330 days). The 22 patients had received a median cumulative mitotane dose of 142 g (range: 66–270) after 1 month. 272 g (range: 112–405) after 2 months, and 405 g (range: 157–546) after 3 months.

A therapeutic plasma mitotane level of 14 mg/l or over was reached at least once during the first 3 months of therapy by 10/22 patients (45%). Therapeutic levels were measured in six patients (27%) at 1 month, in seven patients (32%) at 2 months, and in seven patients (32%) at 3 months (Fig. 1A). A minimum mitotane level of 4 mg/l at 1 month and 11 mg/l at 2 months was measured in the subgroup of patients who achieved a therapeutic level at 3 months. Four other patients reached therapeutic mitotane levels after 3 months (months 5 and 14) but before alternative therapeutic options were given. Finally, two patients reached the therapeutic levels at the time of combined mitotane and chemotherapy (months 6 and 27; Fig. 1B). Toxic mitotane levels were reached in two patients (9%) at month 2 and month 6 respectively. Pretoxic levels were reached in one (4.5%) patient at month 2.

Parameters correlated with the early therapeutic plasma mitotane level

No correlation was found between the parameters listed and early achievement of a therapeutic plasma level. The median cumulative mitotane dose in patients who reached a therapeutic mitotane level was 276 g (range: 87–741). No significant correlation was found between the cumulative mitotane dose and the plasma mitotane level.

Tolerance of the high-dose mitotane strategy

Treatment toxicities are detailed in Table 2. The most frequent adverse event was digestive toxicity (grade 1 or 2). Onset of digestive toxicity was not related to plasma mitotane level. Mitotane was transiently discontinued in 11/22 patients (50%) due to toxicity, for a median time of 7 days (range: 7–180), after a median time of 2.5 months (range: 1–11 months). At the time of withdrawal, the median plasma mitotane level was 20 mg/l (range: 2.6–31) and 5/11 patients (45%) had a plasma mitotane level <14 mg/l. None of the patients permanently discontinued mitotane due to toxicity. The 11 patients who transiently discontinued mitotane treatment experienced grade 1 or 2 digestive toxicity (73% anorexia, 73% nausea, 64% vomiting, 36% diarrhea, and 9% abdominal pain). Furthermore, cholestasis was observed in eight patients (73%) and grade 1 cytolysis in one patient (9%). Only three of these 11 patients had reached a plasma level >30 mg/l. Two of these three patients also experienced neurological toxicity: grade 3 ataxia in one (plasma mitotane level of 34 mg/l) and grade 3 disabling vertigo in the other patient (plasma mitotane level of 36 mg/l). The remaining patient did not experience any neurological toxicity despite a plasma mitotane level at 31 mg/l. One patient experienced grade 4 anemia due to erythroblastopenia, but the plasma mitotane level remained at 6.7 mg/l. All toxic effects were reversible.

Four patients (18%) permanently discontinued mitotane treatment after a median time of 12 months (range: 7–24 months) because of tumor progression. At that time, the median plasma mitotane level was 5 mg/l (range: 2.6–15.5).
Table 2 Mitotane toxicity graded according to the National Cancer Institute (NCI) criteria (NCI. NCTAE version 3).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td>Cholestasis</td>
<td>7</td>
</tr>
<tr>
<td>Cytolysis</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>–</td>
</tr>
<tr>
<td>Dyssarhia</td>
<td>1</td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
<td>2</td>
</tr>
<tr>
<td>Vision trouble</td>
<td>1</td>
</tr>
<tr>
<td>Memory trouble</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>3</td>
</tr>
</tbody>
</table>

Discussion

There is no consensus regarding the optimal strategy for initiating mitotane therapy in ACC patients. In addition, no randomized study is planned to solve this issue. Therefore, comparison of historical studies and implementation of prospective studies like this study or the ongoing stratified PK-Lysodren trial provides the best evidence possible. To date, plasma mitotane level is the only confirmed predictor of tumor response to mitotane therapy (27). The free-of-charge LysoSafe service allows the centralization of plasma mitotane measurement, and thus recommendations based on this endpoint are easily applicable in Europe. To the best of our knowledge, this study in ACC patients is the first to provide monthly mitotane measurements during the first 3 months of therapy.

In our study, 45% of ACC patients (ten out of 22) reached a plasma mitotane level in the therapeutic range within the first 3 months with high-dose mitotane strategy. Therapeutic mitotane levels were maintained for at least two measurements during the first 3 months of therapy in 32% of ACC patients. In total, 64% of ACC patients (14 out of 22) reached the therapeutic plasma level before another therapeutic option was initiated, at a median time of 2 months (range 1–14 months) after the initiation of treatment.

A median dose of 6 g/day was given during the first 2 weeks of treatment and 68% of patients who were given 4–6 g/day were able to maintain the same dose for a median of 4 weeks. A higher dose (above 6 g/day) could only be maintained for a few days and should, therefore, not be recommended on a routine basis.

Five studies have provided data on patient tolerance to mitotane either as a single drug (7, 9, 12, 28) or in combination with chemotherapy (29). It is interesting to note that single agent mitotane could be administered at higher doses (median 6 g/day (7) or 4–8 g/day (9, 12)) than when combined with chemotherapy (1–4 g/day (29)).

In addition to our previous reports, only a few studies analyzed the potential relationships between the mitotane dose and plasma levels during the first month of treatment (11, 20, 24, 28). In one study, all eight patients treated with 1–3 g/day and all patients who ingested at least 283 g of mitotane achieved therapeutic plasma mitotane levels within a median time of 3–5 months (20). In another study on 17 patients treated with a median daily dose of 4 g (28), all patients achieved a therapeutic plasma mitotane level after a maximum of 9 months, and 47% achieved therapeutic plasma levels at 3 months. In this study, using a 6 g/day median mitotane dose, we report similar results at 3 months. However, only 64% of the patients reached a therapeutic plasma mitotane level after the ingestion of a median cumulative mitotane dose of 405 g, a percentage that is similar to that obtained in our previous study (12). Of note, this inability to reach the therapeutic plasma mitotane level in some patients has already been reported in previous studies (9, 15).

Indeed, digestive absorption of the drug is only 40% of the ingested dose, and changes in the galenic presentation of the drug may also affect its bioavailability (25).

Therefore, our study does not provide firm evidence of the superiority of a high-dose mitotane regimen during the first 3 months of therapy. However, a high-dose strategy defined as dosage above or equal to 4 g/day could still be beneficial in shortening the treatment interval required to achieve a therapeutic plasma

Figure 2 Recommendation for mitotane initiation high-dose strategy during the first 2 months of treatment: algorithm of Gustave Roussy Institute.
mitotane levels (23). Indeed, 27% of the patients in this study achieved a therapeutic plasma level of mitotane at 1 month.

Grade 3 or 4 adverse events were observed in 13% of patients and the drug was temporarily discontinued due to toxicity in 50% of patients. Although 22% of patients permanently discontinued mitotane in one old study (7), results similar to ours of only transient discontinuation have also been reported by another team (28). This suggests that the management of mitotane therapy could benefit both from experienced physicians and from constant mitotane monitoring. To the best of our knowledge, mitotane-induced erythroblastopenia is described for the first time in this study. As the erythroblastopenia event recovered after mitotane was stopped and also recurred early after mitotane therapy was resumed, we consider this side effect to be directly related to mitotane administration. Mainly digestive toxicity was observed, even when plasma mitotane levels remained below 14 mg/l (50% of cases). Three patients (13.6%) exhibited toxic mitotane levels, among whom two (9%) experienced grade 3–4 neurological toxicity. These results are in accordance with two previous studies in which such toxicities were observed in 41 and 12% of patients treated with a lower dose of mitotane (21, 28). We therefore consider that side effects related to the high-dose mitotane strategy appeared sooner in our study but are still manageable with the help of plasma mitotane measurements.

In a previous study, we found that the mitotane dose could explain 38% of plasma mitotane levels, which suggests that other factors are involved in regulating plasma levels of mitotane (11). No relationship between plasma mitotane level and the mitotane dose was found in this study, suggesting that the dose is only one of the parameters that may affect mitotane plasma level. Our hypothesis is that the benefits of a high-dose mitotane strategy may be restricted to a subgroup of patients characterized by their capacity to absorb, metabolize, and store mitotane in an efficient manner. However, such mechanisms remain to be elucidated. For instance, mitotane is bound to lipoproteins in the plasma (30, 31) and access to target tissue such as the brain is dependent on lipoprotein profiles (32). Furthermore, mitotane has been shown to affect lipoprotein profiles by increasing low-density lipoprotein and high-density lipoproteins (28). However, the relationship between mitotane access to target tissues and the lipoprotein profile has yet to be analyzed.

Interestingly, 86% (6/7) of the patients who were within the therapeutic plasma mitotane range at 3 months had already reached the level at 1 or 2 months. In addition, they represent 43% (6/14) of patients who reached the therapeutic plasma mitotane level during the entire study. Therefore, another potential interest of the high-dose strategy could be to help selection of patients with the most favorable pharmacokinetic profile. Indeed, a minimum plasma mitotane level of 4 or 11 mg/l was reached at month 1 or 2 in all patients who achieved the therapeutic plasma mitotane level at 3 months. In contrast, 50% (6/12) or only 8% (1/12) of patients unable to achieve the therapeutic plasma mitotane level during the first 3 months experienced plasma mitotane level above 4 or 11 mg/l at month 1 or 2 respectively. Therefore, we recommend that a high-dose strategy defined by a mitotane dose initiation between 4 and 6 g/day could be given during the first 6 weeks of therapy and could only be maintained if the toxicity profile is acceptable and if minimum plasma mitotane levels of 4 or 11 mg/l are obtained during the first or second month of therapy. Such cut-off values require confirmation in larger prospective studies. In case of consistently low plasma levels of mitotane and advanced ACC, the place of a combined cytotoxic chemotherapy should be discussed, as has been recently proposed (33). Additional parameters like prognostic parameters, the rate of tumor progression, and anatomical locations of tumors may also be characterized to refine the best strategy. Other options like locoregional therapies may represent interesting alternatives in the case of favorable prognostic parameters and appropriate tumor presentation (1, 34). Based on these results, an expert opinion in the management of mitotane treatment is presented in Fig. 2.

In conclusion, a high-dose strategy defined as a median dose of 6 g/day of mitotane over 6 weeks allowed 27% of ACC patients to reach the 14 mg/l therapeutic plasma mitotane level within 1 month, and 45% of patients within 3 months. If this strategy is adopted, we suggest that mitotane dose is readjusted according to plasma mitotane levels at 1 or/and 2 months and patient tolerance.

Declaration of interest
We declare that E Baudin is coinvestigator of the PK Lysodren trial and received grants from HRA.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Acknowledgements
Thanks to Lorna Saint-Ange for editing.

References
High-dose mitotane strategy in ACC

Eur J Endocrinol (2012) 166

267


motherapy in metastatic adrenocortical carcinoma. Endocrine-

Related Cancer 2010 17 797–807. (doi:10.1677/ERC-09-0341)

Nelson AA & Woodard G. Severe adrenal cortical atrophy (cysto-

tic) and hepatic damage produced in dogs by feeding 2,2-

bistiparachlorophenyl-1,1-dichloroethane (DDD or TDE). Archives

of Pathology 1949 48 387–394.

Bergenthal DM & Dao TL. Management of Addison’s disease in

adenalecтомized patients. Bulletin of the New York Academy of

Medicine 1953 29 295–306.

van Slooten HMA, van Seters AP & Smeerik D. The treatment of

adrenocortical carcinoma with o,p’DDD: prognostic implications

of serum level monitoring. European Journal of Cancer & Clinical


Terzolo M, Pia A, Berrutti A, Osella G, Ali A, Carbone V, Testa E,

Dognitti L & Angeli A. Low-dose monitored mitotane treatment

achieves the therapeutic range with manageable side effects

in patients with adrenocortical cancer. Journal of Clinical


1210/cjc.85.6.2234)

Terzolo M, Angeli A, Fassnacht M, Daﬀara F, Tauchmanova L,

Conta PA, Rossetto R, Buci L, Sperone F, Grossrubatscher E,

Reimondo G, Bollito E, Papotti M, Saeger W, Hahner S, Kocshler AC,

Arvat E, Ambrosi B, Loli P, Lombardi G, Mannelli M, Bruzzi P,

Matzer F, Alloio B, Doglotti I & Berrutti A. Adjuvant mitotane

treatment for adrenocortical carcinoma. New England Journal


Stigliano A, Cerquetti L, Borro M, Gentile G, Bucco B, Misiti S,

Piergrossi P, Brunetti E, Simmaco M & Toscano V. Modulation of

protemic proﬁle in H295R adrenocortical cell line induced by


1677/ERC-07-0003)

Abraham J, Bakke S, Rutt A, Meadows B, Merino M, Alexander B,

Schrum D, Bartlett D, Choyke P, Robey B, Hung E, Steinberg SM,

Bates S & Fojo T. A phase II trial of combination chemotherapy and

surgical resection for the treatment of metastatic adrenocortical

carcinoma: continuous infusion doxorubicin, vincristine, and

etoposide with daily mitotane as a P-glycoprotein antagonist.


Faggiano A, Lebouilleux S, Young J, Schlumberger M & Baudin E.

Rapidly progressing high o,p’DDD doses shorten the time required

to reach the therapeutic threshold with an acceptable tolerance:


Moolenaar AJ, van Slooten H, van Seters AP & Smeerik D. Blood

levels of o,p’DDD following administration in various vehicles

after a single dose and during long-term treatment. Cancer


BF00258213)

Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS,

Beuschlein F, Terzolo M, Muller HH, Hahner S & Alloio B. Limited

prognostic value of the 2004 International Union Against Cancer

staging classification for adrenocortical carcinoma: proposal for a


1002/cncr.24030)

Hermsen IG, Fassnacht M, Terzolo M, Houterman S, den Hark JG,

Lebouilleux S, Daﬀara F, Berrutti A, Chadarevian B, Schlumberger M,

Alloio B, Hahner HR & Baudin E. Plasma concentrations of o,p’DDD,


(doi:10.1210/jc.2010-2676)

Berruti A & Terzolo M. Prospective evaluation of mitotane toxicity in adrenocortical cancer patients treated adjuvantly. *Endocrine-Related Cancer* 2008 **15** 1043–1053. (doi:10.1677/ERC-08-0103)


Received 24 June 2011

Revised version received 28 October 2011

Accepted 1 November 2011

www.eje-online.org