Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center

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Abstract

Context: Alternatives to transsphenoidal pituitary surgery may be required in Cushing’s disease (CD) as a first- or second-line treatment. Mitotane is a potent anti-cortisolic drug but has been rarely investigated in the treatment of CD.

Objective: Evaluation of the efficacy and tolerance of mitotane in CD patients.

Design and setting: Retrospective analysis of 76 patients treated with mitotane from 219 patients diagnosed with CD between 1993 and 2009 in a single center.

Main outcome measure: Remission was defined as normalization of 24-h urinary free cortisol (24-h-UFC).

Results: Remission was achieved in 48 (72%) of the 67 long-term treated patients, after a median time of 6.7 (5.2–8.2) months. Mean plasma mitotane concentration at the time of remission was 10.5 ± 8.9 mg/l, with a mean daily dose of 2.6 ± 1.1 g. A negative linear relationship was observed between plasma mitotane concentration and 24-h-UFC (P ≤ 0.0001). Seventeen of 24 (71%) patients with durable remission subsequently experienced recurrence, after a median time of 13.2 (5.0–67.9) months. At the time of treatment discontinuation, ACTH concentration was statistically associated with a lower recurrence probability (hazard ratios 0.57 (0.32–1.00), P < 0.05). Intolerance leading to treatment discontinuation occurred in 19 patients (29%). A pituitary adenoma became identifiable during mitotane treatment in 12 (25%) of the 48 patients with initial negative pituitary imaging allowing subsequent transsphenoidal surgery.

Conclusion: Mitotane is useful at different stages of CD. Mitotane dose adjustment based on plasma concentration monitoring and side effects could control hypercortisolism in the majority of CD patients.

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Introduction

Cushing’s syndrome is associated with a high morbidity and can be lethal when not treated. Its most frequent cause is Cushing’s disease (CD). The first-line treatment for CD is transsphenoidal surgery (TSS) that selectively removes the causative corticotroph adenoma (mostly microadenomas) (1), but despite modern imaging by magnetic resonance imaging (MRI), a pituitary tumor is not visible in 35–65% of patients (2). Immediate disease remission is achieved in about 60–80% of patients after pituitary surgery (3, 4) but late recurrence occurs in 5–20% of patients (5).

Alternative therapeutic approaches are therefore needed for CD, either as first-line treatment, after failure of pituitary surgery, or in the case of CD recurrence. Pituitary irradiation is one alternative but, despite substantial progress in radiotherapeutic methods, efficacy is not immediate and there are significant side effects (6). Bilateral adrenalectomy immediately controls excess cortisol but requires lifelong steroid-substitution therapy. Moreover, after bilateral adrenalectomy, the corticotroph pituitary tumor may progress, requiring additional targeted pituitary treatment (7). The main pharmacotherapeutic treatments for CD are adrenal-blocking drugs such as metyrapone, ketoconazole, and 1,ortho-1,para’-dichloro-diphenyl-dichloro-ethane (o,p’DDD), also termed mitotane (3, 8, 9, 10). Other drugs that directly target ACTH secretion have recently been developed but induce only limited and/or transient remission (11, 12, 13, 14) of CD.

The anti-cortisolic effect of mitotane was first described in dogs and subsequently in humans in 1961 (15, 16). In addition to enzyme-inhibitory activity against 11β-hydroxylation and cholesterol side chain cleavage, mitotane has a strong adrenolytic effect that
confers long-lasting activity and could limit the escape phenomenon observed with other anti-cortisolic drugs (17). There is now evidence for the anti-proliferative and anti-secretory effects of mitotane in adrenocortical cancer (18, 19, 20), but there are no recent data on its long-term efficacy or safety in the treatment of CD. The largest study to date was published from our center in 1979 and included 62 patients treated with mitotane, of whom 24 also received pituitary irradiation (21). The aim of the current study was to analyze the efficacy and side effects of mitotane as a first- or second-line treatment in patients with CD in a single center.

Materials and methods

Patients

A total of 76 consecutive patients in the endocrinology department of Cochin Hospital diagnosed with CD between January 1993 and December 2009 and treated with mitotane were analyzed retrospectively. These patients are part of a cohort of 248 patients with ACTH-dependant Cushing’s syndrome followed during the same period. This population was different from that previously studied in our center (21). We excluded patients with proven or suspected ectopic ACTH secretion (29 patients) and patients with mitotane treatment initiated outside our center and for whom no data were available for the treatment period (ten patients). Of the 76 patients studied, none had previously received radiotherapy, except one patient who was treated with mitotane for persisting CD 3 years after gamma knife radiosurgery.

Before 2004, mitotane was administered orally with 500 mg capsules (mitotane APHP) provided by the Assistance Publique-Hôpitaux de Paris pharmacy. From 2004 onward, oral mitotane was administered in the form of 500 mg Lysodren tablets (HRA Pharma, Paris, France). These two mitotane formulations have different absorption rates: three 500 mg tablets of the APHP formulation are considered equivalent to one 500 mg Lysodren tablet (22). Thus, for clarity, the Lysodren-equivalent dose is used in this study. For doses up to 4 g/day, mitotane was administered in three daily doses and gradually tapered to the minimal dose required to maintain remission. The majority of patients began their treatment in hospital for close monitoring and were reevaluated almost every 3 months during the first year of treatment. Since the aim was to block and then substitute, almost all patients received concomitant hydrocortisone replacement except for those with persisting hypocortisolism. The study was performed according to the French rules for noninterventional monocentric clinical record analysis with approval by the national committee for clinical computed database management (CNIL).

Diagnosis of CD

ACTH-dependent Cushing’s syndrome was diagnosed on the basis of classical clinical findings and laboratory criteria (23), including urinary free cortisol (UFC) excretion above 90 μg/24 h (248 nmol/24 h), midnight plasma cortisol above 75 ng/ml (207 nmol/l) or midnight salivary cortisol above 2 ng/ml (5.52 nmol/l), and/or plasma cortisol after overnight 1 mg dexamethasone suppression test above 18 ng/ml (50 nmol/l), and unsuppressed plasma ACTH.

The pituitary origin of ACTH was determined with various levels of certainty. ‘Proven’ CD (56 patients) was defined by histological confirmation of corticotroph adenoma and/or postsurgical corticotroph deficiency and/or central-to-peripheral gradient in bilateral inferior petrosal sinus venous sample. ‘Highly suspected’ CD (20 patients) was defined by the absence of the preceding criteria but the presence of at least one dynamic test result consistent with CD among corticotropin-releasing hormone stimulation test, metyrapone stimulation test, or high-dose (8 mg) dexamethasone suppression test, along with no evidence for an ectopic source of ACTH during the follow-up.

Endocrine follow-up, remission, and recurrence criteria

Clinical and hormonal data were analyzed before mitotane treatment. 3–6 months after the beginning of treatment, and then yearly. 24-h-UFC was assayed off-hydrocortisone substitutive therapy with medical surveillance. Remission at follow-up was defined as either normalization of 24-h-UFC (<90 μg) or hypocortisolism. Hypocortisolism was defined as a morning plasma cortisol concentration <50 ng/ml (138 nmol/l) or <210 ng/ml (580 nmol/l) after 250 μg ACTH-stimulation test using Synacthen. Recurrence of hypocortisolism after treatment withdrawal was defined as an elevated 24-h-UFC (>90 μg), with Cushing’s syndrome’s clinical symptoms, and the need for a new therapeutic intervention.

Biological assays and imaging

Cortisol and ACTH were assayed as previously reported (24, 25). The mitotane plasma concentration assay was used routinely in our center from the year 2000 and was measured using an isocratic HPLC. Samples were deproteinated with cold acetone, and mitotane concentrations were quantified using a diode-array detector with 1.1-dichloro,2,2-bis (P-chlorophenyl) ethylene as an internal standard (26).

All patients underwent pituitary MRI before mitotane treatment and had regular MRIs during the follow-up. Pituitary MRI scans were performed with coronal and sagittal T1 weighting, with and without enhancement, and with coronal T2 weighting. When the initial MRI...
was negative but the MRI during follow-up had revealed an adenoma or if the tumor size increased during treatment, we performed a second reading of MRIs; a single radiologist analyzed at the same time, retrospectively and without clinical information on outcome and current treatment of the patients concerned, all pituitary MRIs in chronological order for each patient. The results were compared with those obtained at the time at which the MRI scans were actually performed.

Statistical analysis

Data are reported using median and range, or percentages as appropriate. Given the non-normal distribution of several variables and the small numbers of subjects in some groups of interest, we used nonparametric statistical methods to study the relationship between variables when appropriate (Fisher’s exact test, Wilcoxon test, and pairwise Wilcoxon test). We used two-tailed tests, and P values <0.05 were considered significant.Remission, recurrence, and time-to-event were estimated by the Kaplan–Meier method, with follow-up starting at the beginning of mitotane treatment for remission. At the time of treatment withdrawal, the patient was censored. For recurrence, follow-up started at the end of the treatment in patients achieving remission. The predictive values of clinical and biological criteria for remission, intolerance, and relapse were evaluated using Cox’s proportional hazards regression models, which were used to estimate crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs). The relationships between 24-h-UFC and mitotane current dose or mitotane plasma concentration were assessed using linear mixed models adapted for repeated measures (27). The dependent variable (24-h-UFC) was log-transformed as residuals departed from normality. Statistical analysis was performed using SAS version 9.2 (SAS institute, Inc., Cary, NC, USA).

Results

A total of 76 patients were treated with mitotane for CD diagnosed between January 1993 and December 2009 in Cochin Hospital. The main characteristics of these patients are described in Table 1. Among them, 49 patients were treated with mitotane as a first-line treatment, while 27 as second-line treatment, i.e. after TSS.

Remission and its determinants

Nine patients received mitotane very transiently, as preparation for planned pituitary surgery was temporarily delayed due to severe hypercortisolism. These patients were excluded from the efficacy analysis. Among the 67 other patients, remission was obtained in 48 (72%) patients after a median time of 6.7 months

| Table 1 Main characteristics of the 76 patients treated with mitotane, either as a first-line treatment or as a second-line therapy after pituitary surgery. Data are expressed as number (percentage) or median (range). The mean daily dose was calculated by dividing the cumulative dose by treatment duration in days. |
| Baseline characteristics | First-line treatment (n=49) | Second-line treatment (n=27) |
| Gender: women/men | 36 (73)/13 (27) | 23 (85)/4 (15) |
| Age at diagnostic (years) | 39 (14–71) | 34 ± 12 (14–61)* |
| Baseline hormonology | | |
| Urinary cortisol (µg/24 h) | 383 (84–3750) | 240 (122–1094)* |
| Plasma ACTH (pg/ml) | 65 (16–2100) | 51 (20–216)* |
| Negative baseline MR imaging | 39 (80) | 15 (56)* |
| Indication | | |
| No pituitary adenoma | 39 (80) | – |
| Invasive pituitary adenoma | 3 (6) | – |
| Pituitary surgery failure | – | 16 (59) |
| Relapse after pituitary surgery | – | 9 (33) |
| Preparation before surgery | 7 (14) | 2 (8) |
| Treatment characteristics | | |
| Initial daily dose (g/day) | 2.7 (0.3–4.5) | 2.0 (1.0–8.0) |
| Treatment duration (months) | 6.9 (0.3–114.9) | 16.4 (0.8–66.9) |
| Cumulative dose (g) | 543 (43–4435) | 1076 (46–5676)* |
| Mean daily dose (g/day) | 2.5 (1.1–4.3) | 2.4 (0.9–6.1) |
| Bilateral adrenalectomy during follow-up | 19 (39) | 10 (37) |
| Pituitary radiotherapy during follow-up | 4 (8) | 5 (19) |

MR, magnetic resonance. *P<0.05 compared with first-line treatment group.

(95% CIs 5.2–8.2; Fig. 1). Of the 19 patients who did not achieve remission, treatment was withdrawn due to lack of efficacy in ten patients (after a median period of 7.9 months) and due to intolerance in nine patients (after a median period of 2.2 months). Of note, in the ten patients who discontinued treatment due to lack of efficacy, there was a mean decrease in 24-h-UFC of 50%.

Univariate analysis was performed to identify predictive factors of remission and no significant difference was observed between the mitotane first- and second-line treatment groups. Similarly, patient age, gender, weight or BMI, initial mitotane dose, severity of baseline hypercortisolism, and baseline plasma ACTH concentration were not significant predictors of response to therapy.

Clinical and hormonal course with mitotane

The main hormonal and metabolic parameters, before and during mitotane treatment, in the patients who experienced remission are shown in Table 2. Mean ACTH levels increased from 67.8 ± 65.8 to 221.3 ± 180.9 pg/ml (P<0.0001). There was a statistically significant improvement in all metabolic parameters after 6 months of treatment, except in systolic blood pressure and lipid profile. Total cholesterol increased

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due to increases in LDL-cholesterol from 3.5±1.1 to 4.7±2.2 mmol/l \((P<0.05)\) and HDL-cholesterol from 1.6±0.5 to 2.0±0.7 mmol/l \((P<0.05)\). However, the LDL/HDL-cholesterol ratio remained stable, from 2.4±1.4 to 2.4±1.5 \((P=0.43)\). Triglycerides were also slightly increased from 1.7±1.8 to 1.9±1.1 mmol/l \((P<0.01)\). Of note, seven patients were being treated with statins at the start of mitotane treatment and 13 patients commenced statin therapy during the treatment.

**Relationship between plasma mitotane concentrations and remission**

Plasma mitotane was routinely measured in 36 patients, representing a total of 108 distinct measures. At the time of remission, mean plasma mitotane concentration in the remission group was 10.6±5.2 mg/l \((n=24)\), with a mean daily dose of 2.7±1.2 g/day.

There was no statistically significant relationship between plasma mitotane concentration and current daily dose at any time-point. Moreover, no statistically significant relationship was found between 24-h-UFC and concomitant daily dose of mitotane.

However, a negative linear relationship was observed between plasma mitotane concentration and 24-h-UFC: an increase of 1 mg/l plasma mitotane concentration was associated with a decrease of 10.4 μg for 24-h-UFC. Owing to a mild departure from normality in the residuals, 24-h-UFC was log-transformed. This transformation resulted in a highly significant negative linear relationship of 24-h-UFC with plasma mitotane concentrations \((P<0.0001)\). There were 73 concomitant measures of mitotane plasma concentration and 24-h-UFC. Patients with a mitotane plasma concentration above 8.5 mg/l did not have abnormal concomitant 24-h-UFC values (Fig. 2).

**Adverse effects and clinical tolerance to mitotane**

Adverse effects that occurred during mitotane treatment were divided into two groups: serious intolerance that led to treatment discontinuation and mild intolerance where treatment was continued. The most frequent adverse effects were gastrointestinal (47% of patients) and neurologic intolerance (30% of patients; Table 3). The retrospective nature of the study did not allow investigation of whether these adverse events were treatment related.

A total of 19 patients showed serious adverse effects leading to treatment withdrawal, accounting for 28% of the 67 patients who received mitotane not only for preparation of surgery. Of these 19 patients, ten had already reached remission at the time of discontinuation. Univariate analysis showed that none of the baseline characteristics studied (first- or second-line treatment, age, gender, weight, BMI, starting dose of mitotane, mitotane formulation: mitotane APHP or Lysodren, and severity of hypercortisolism)
were statistically associated with the occurrence of serious intolerance.

Only two patients had a mitotane plasma concentration above 20 mg/l (22 and 25 mg/l) during the course of treatment. In one of these patients, this was associated with signs of neurotoxicity.

**Characterization of hypercortisolism recurrence after mitotane discontinuation**

Among the 48 patients who achieved remission, four patients were still being treated with mitotane at the time of this analysis. Treatment was discontinued in the remaining 44 patients for different reasons. In 18 patients, another treatment was immediately performed: in this group of patients, mitotane was discontinued because of pituitary adenoma visualization during the imaging follow-up allowing TSS in eight of them, relapse of hypercortisolism under mitotane treatment in five of them (for these five patients, the mitotane daily dose had to be reduced after having achieved initial remission because of poor clinical tolerance at higher doses), and other reasons like patient’s choice or, in five of them, moving to a country without mitotane available.

The other patients (n=26) had discontinued treatment without an alternative treatment because of controlled disease (n=13), serious intolerance (n=9), and pregnancy wish (n=4). Among these patients, 24 were at risk of recurrence, i.e. in remission, at the time of mitotane discontinuation, without another therapeutic intervention, and not lost to follow-up. At the time of mitotane discontinuation, 18 of these 24 patients (75%) presented adrenal insufficiency. Median follow-up duration after treatment discontinuation was 71 months (29–126). During this follow-up, 17 (71%) patients showed recurrence of hypercortisolism. The median time-to-recurrence after mitotane discontinuation was 13.2 months (5.0–67.9, 95% confidence limits; Fig. 3).

Univariate analysis showed that recurrence was not statistically associated with age, gender, last dose of mitotane, last plasma mitotane concentration, total treatment duration, or cumulative dose of mitotane. Adrenal insufficiency at the time of treatment withdrawal was not statistically predictive of recurrence nor were 24-h-UFC or morning plasma cortisol concentrations. Conversely, a higher ACTH concentration at the time of treatment withdrawal was significantly associated with a lower probability of recurrence (HR 0.57 (0.32–1.00), P=0.05), but this relation was not a linear one. At the time of treatment withdrawal, compared with patients with plasma ACTH ≤114 pg/ml (the first quartile of the 24 patients at risk of recurrence), patients with plasma ACTH >114 pg/ml had an almost statistically significant lower probability of recurrence (HR 0.36 (0.13–1.02), P=0.05).

**Evolution of pituitary imaging during mitotane treatment**

Despite a negative MRI before treatment, in 12 patients, a pituitary adenoma became apparent upon MRI during or at the end of mitotane treatment (‘emergent pituitary adenoma’), after a median time of 10.9 (range: 3.8–94.6) months. Ten of these 12 patients were treated with mitotane as first-line treatment, accounting for 25.6% of the 39 patients with no initial adenoma visualization and mitotane as first-line treatment. For the remaining two

**Table 3** Main adverse effects observed during mitotane therapy in the 76 patients who received the treatment. Gastrointestinal signs included anorexia, nausea/vomiting, and diarrhea. Neurologic signs included dysarthria, ataxia, confusion, dizziness, and paresthesia. Mild neutropenia defined as a neutrophil count between 1000 and 1500/mm³. Other side effects: one patient developed hemolysis and hemostasis abnormality and one patient developed acute depression.

<table>
<thead>
<tr>
<th>Mild intolerance</th>
<th>Serious intolerance</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal signs</td>
<td>36 (47.4%)</td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>13 (17.1%)</td>
</tr>
<tr>
<td>&gt; ULN</td>
<td>11</td>
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<tr>
<td>&gt; 3× ULN</td>
<td>2</td>
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<tr>
<td>Increased GGT</td>
<td>36 (47.4%)</td>
</tr>
<tr>
<td>&gt; 3× ULN</td>
<td>24</td>
</tr>
<tr>
<td>&gt; 5× ULN</td>
<td>12</td>
</tr>
<tr>
<td>Neurologic signs</td>
<td>23 (30.3%)</td>
</tr>
<tr>
<td>Lipid disorders</td>
<td>54 (71.1%)</td>
</tr>
<tr>
<td>LDL-cholesterol (&gt; 3.35 mmol/l)</td>
<td>15 (19.7%)</td>
</tr>
<tr>
<td>LDL-cholesterol (&gt; 5.16 mmol/l)</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>Triglycerides (&gt; 2.28 mmol/l)</td>
<td>25 (32.9%)</td>
</tr>
<tr>
<td>Mild neutropenia</td>
<td>5 (6.6%)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Gynecomastia (men)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.6%)</td>
</tr>
</tbody>
</table>

ULN, upper limit of normal range.
However, the target concentration for 20 mg/l is recommended in adrenocortical cancer and a target plasma concentration between 14 and 30 mg/l is recommended in adrenocortical cancer (28, 29, 30). The narrow therapeutic range of mitotane is well known, particularly in controlling hypercortisolism. The monitoring of plasma mitotane concentrations is of particular interest in controlling hypercortisolism. These results are consistent with the majority of other published findings. Indeed, the largest studies published 30 years ago (21, 35) reported a remission rate of 80%, but in association with pituitary irradiation in most cases, and with less precise remission criteria than the criteria used in our study. These data are obviously no longer relevant in assessing mitotane efficacy for CD management, as modern pituitary imaging and pituitary surgery emerged after these studies. More recent studies have been relatively small, including less than ten patients (36).

Although TSS is currently the only curative treatment for CD, it is often difficult to perform due to the lack of pituitary adenoma visualization in 35–65% of patients. Invasive pituitary adenomas are not accessible for complete resection. Moreover, immediate and long-term remission are not always achieved with TSS. In a recent study, the recurrence rate of CD after TSS due to microadenoma was 25%, with a median time to recurrence of 39 months (4). In these cases, a second TSS is possible, but the immediate remission rate is lower (37, 38).

There is therefore a need for alternative or complementary therapeutic approaches. Other studies have reported various remission rates with medical

**Figure 3** Kaplan–Meier estimation of recurrence in the 24 ‘at-risk’ patients after mitotane was discontinued.
treatments: 75% remission with short-term metyrapone (8), 51% with ketoconazole (10, 39) and 25–35% of 24-h-UFC normalization with the pituitary-targeted agent cabergoline (11, 40). In very severe forms of Cushing’s syndrome, combination therapy with metyrapone, ketoconazole, and mitotane have been used successfully (41). Another pharmacologic agent, pasireotide, has been investigated in a phase III randomized double-blind trial comparing two doses in CD (14). Preliminary results showed a limited remission rate of only 29% with pasireotide monotherapy, with disturbance of glucose homeostasis as the main adverse event (13). With these different pharmacological approaches, a combination of several medications often seems necessary to adequately control CD (13, 40). In our study, complete remission was achieved in 48 patients with mitotane monotherapy.

Other second-line therapeutic options for CD are radiotherapy or radiosurgery, but these options have delayed efficacy and remission rates of about 50%. Finally, the ultimate option for CD treatment is bilateral adrenalectomy, leading to definitive adrenal deficiency requiring lifetime steroid replacement therapy.

Owing to the long follow-up period (mean time 97 months, range 6.3–192 months), we were able to assess the long-term management of CD patients treated with mitotane. After remission, some patients subsequently underwent TSS. In the subgroup of patients that were in remission, and whose mitotane treatment had been discontinued without further therapeutic intervention, the overall recurrence rate was 71%. Seven out of 24 patients (29%) did not experience a recurrence of hypercortisolism, despite treatment discontinuation. Indeed, unlike steroidogenesis inhibitors, mitotane is also cytotoxic for the adrenocortical cells. This might explain, in a subset of patients, a long lasting effect due to this adrenolytic effect. Only a high plasma ACTH concentration at the time of treatment withdrawal seems to be associated with a lower probability of recurrence. We hypothesize that a higher ACTH concentration is a reflection of the extent of adrenal suppression. This might be due to increased tumoral ACTH secretion secondary to reduced cortisol feedback on the tumor cells and, to a lesser extent, reactivation of the normal corticotroph cells with cortisol excess correction.

During follow-up, at least 25% of patients with a negative initial MRI had later MRI visualization of a pituitary adenoma after mitotane treatment. This is particularly interesting as mitotane treatment could allow control of cortisol secretion until better visualization of the causal pituitary tumor is possible.

Regarding the tolerance of mitotane, we observed frequent mild side effects, mainly affecting the gastrointestinal and nervous systems, as previously reported (42). However, these adverse effects could be managed by tapering the mitotane dose and/or with additional symptomatic treatment in nearly three-quarters of cases. In some cases, these side effects could have been related to insufficient steroid replacement in parallel with mitotane treatment. Mild elevation of γ-glutamyltransferase levels was quite frequent, but significant transaminase elevation (above three times the upper limit of normal range) was only noticed in three patients. No cases of hepatocellular deficiency occurred. Finally, mitotane was associated with a mild increase in LDL- and HDL-cholesterol as previously reported (42, 43). This has been attributed to the inhibition of cytochrome P450 (44).

Of the 76 patients studied, six women underwent therapeutic abortion due to pregnancy occurring under treatment or immediately after mitotane discontinuation. Four women had normal pregnancies after treatment discontinuation and a sufficient latency period, resulting in healthy babies with no identifiable malformities.

In conclusion, this retrospective study of a large cohort of CD patients highlights the efficacy and tolerance of mitotane therapy in this rare disease. Treatment with mitotane is useful in the management of different stages of the disease, either as a first-line therapy when pituitary surgery is not appropriate or because of the severity of hypercortisolism, or as a second-line therapy after TSS failure or recurrence of CD. The hormonal control of CD with mitotane therapy is highly associated with the mitotane plasma concentration and its monitoring would help to reach efficacy and manage tolerance.

Declaration of interest

J Bertherat has been involved as a clinical investigator in trials in Cushing’s syndrome sponsored by Novartis.

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