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Original article

Efficacy and safety of mitotane in the treatment of adrenocortical carcinoma: A retrospective study in 34 Belgian patients

Efficacité et sécurité du mitotane dans le traitement de l'adénocarcinome corticosurrénalien : une étude rétrospective chez 34 patients belges

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Abstract

Objectives. – Evaluation of patient characteristics and mitotane use in the treatment of adrenocortical carcinoma (ACC) over a 4-year period in Belgium. *Material and methods.* – This was a multicentre retrospective review of the outcome of 34 patients treated with mitotane for ACC during the period [01/2008–12/2011] (12 diagnosed before and 22 diagnosed during the study period) and evaluated up to 06/2013. *Results.* – Patient and tumour characteristics were consistent with those generally described for ACC. Mean age at diagnosis was 46.5 years, most patients were female (62%), had functioning ACC (65%) and advanced tumours (ENSAT stages III or IV: 82%). Therapeutic mitotane plasma levels (14–20 mg/L) were achieved at least once in 70% of the cohort, after a median of 4 months, and were maintained for more than 2 months in 61% of evaluable patients. Mitotane-related adverse effects were observed in 66% of patients, were never serious, and included gastrointestinal, neurological, neuropsychological, hormonal, dermatologic and metabolic effects. Most patients (88%) discontinued mitotane, mainly due to tumour progression. Multivariate analysis showed that ENSAT stage was a prognostic factor for overall (OS) and disease-free survival (DFS); OS was also influenced independently by achievement of therapeutic mitotane plasma levels for at least two consecutive months. *Conclusion.* – Patient and tumour characteristics were consistent with previously published data. OS and DFS were mostly influenced by ENSAT stage at diagnosis. Achieving therapeutic levels of mitotane for at least two consecutive months seemed to positively influence OS, but such levels were not reached or sustained in some patients.

Keywords: Adrenocortical carcinoma; Mitotane; Adrenal glands; Cancer

Résumé

Buts de l'étude. – Revoir les principales caractéristiques des patients avec un adénocarcinome corticosurrénalien (ACC) traités par mitotane sur une période de 4 ans en Belgique. *Patients.* – Cette étude rétrospective multicentrique a inclus 34 patients traités entre janvier 2008 et décembre 2011 (12 avec diagnostic avant et 22 avec diagnostic pendant la période d'étude) et évalués jusqu'au 30 juin 2013. *Résultats.* – Les caractéristiques de nos patients étaient similaires à celles généralement décrites pour ce type de tumeur (âge moyen au diagnostic : 46,5 ans, prépondérance de femmes [62 %] et de tumeurs sécrétantes [65 %], majorité de stades avancés [stades ENSAT III ou IV : 82 %]). Des concentrations plasmatiques thérapeutiques de mitotane (14–20 mg/L) ont été obtenues au moins une fois chez 70 % des patients après une durée médiane de 4 mois et

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ont été maintenues pendant plus de 2 mois chez 61 % des sujets évaluables. Des effets indésirables liés au mitotane ont été observés chez 66 % des patients (principalement gastro-intestinaux, dermatologiques, neurologiques et neuropsychologiques). La plupart des patients (88 %) ont arrêté le mitotane, principalement en raison de la progression de la tumeur. Une analyse multivariée a montré que le stade ENSAT était un facteur pronostique pour la survie globale (SG) et la survie sans progression ou récidive. La SG était aussi influencée indépendamment par l'obtention de concentrations thérapeutiques de mitotane pendant au moins deux mois. *Conclusion.* – La survie globale était principalement influencée par le stade ENSAT au moment du diagnostic, mais aussi par l'obtention de concentrations thérapeutiques de mitotane pendant au moins deux mois consécutifs. Toutefois, de telles concentrations n'étaient jamais atteintes ou pas de manière soutenue chez plusieurs patients.

Mots clés : Adénocarcinomes corticosurrénaliens ; Corticosurrénalome ; Mitotane ; Glandes surrénales ; Cancer

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumour with an incidence of 1 to 2 per million adults per year [1–4]. These tumours are hormone-secreting in 60–70% of cases, and thus can cause Cushing's syndrome, virilisation or, more rarely, mineralocorticoid excess or feminisation [5,6]. The prognosis of ACC worsens with the stage of the disease. Localised, surgically resectable tumours (i.e. stages I and II of the European Network for the Study of Adrenal Tumors [ENSAT] staging system) have the most favourable prognosis, although they may recur. Advanced and metastatic ACC (ENSAT stages III and IV, respectively) and recurrent ACC have a much poorer outcome [7].

Mitotane (o,p'-DDD) was licensed in Europe in 2004, as an orphan drug (Lysodren®) for the symptomatic treatment of advanced (unresectable, metastatic or recurrent) functioning ACC. Mitotane has direct cytotoxic effects on the adrenal cortex inducing focal degeneration of the zona fasciculata and the zona reticularis. In addition, mitotane inhibits steroid synthesis [8] while stimulating the extra-adrenal metabolism of cortisol by increasing the activity of CYP3A4. Mitotane also exhibits tumour specificity as its adrenolytic effects seem to be enhanced by the presence of CYP11B activity in cortisol-secreting tumours [6]. Recent *in vitro* data have shown that mitotane alters mitochondrial respiratory chain activity by inducing cytochrome-C oxidase defect in human ACC cells [9] and that mitotane inhibits Sterol-O-acyl transferase 1, inducing endoplasmic reticulum stress in ACC cells, in turn leading to apoptosis [10].

Treatment with mitotane is currently indicated in addition to surgery in advanced, metastatic or recurrent ACC [1–4] and also in inoperable patients. The use of mitotane after apparently complete surgery may also be justified for high-grade tumours, as reflected by a high Weiss score, a Ki-67 index above 10% and/or a high mitotic index, and also after R1 resection (microscopic residual tumour), since recurrence almost always occurs in these cases [11–13]. Efficacy of the drug depends on achieving therapeutic plasma levels, ideally mitotane levels greater than or equal to14 mg/L [3,4]. Adverse effects are observed in about 80% of patients and some (especially neurotoxicity) seem to be more frequent when plasma mitotane concentrations exceed 20 mg/L [4,11].

There is currently limited information on the use of mitotane for the treatment of ACC in real-life conditions. This study aimed to evaluate the conditions of mitotane use in patients with ACC in Belgium during a 4-year period, from January 2008 to December 2011. In addition, this study investigated the relationship between the efficacy of mitotane and the plasma concentrations achieved during treatment.

2. Patients

We conducted a multicentre retrospective study in academic centres in Belgium. Only centres with at least 2 eligible patients were invited to participate in the study. Eligible patients had a confirmed diagnosis of ACC and had been treated with mitotane at some time during the period from 01 January 2008 to 31 December 2011. ACC could have been diagnosed before this period. The number of patients with active ACC not treated with mitotane and seen during the same 4-year period was also collected from each centre.

3. Methods

Based on patient's files, the following data were collected for each patient: sex, age at diagnosis, ENSAT stage, number of involved organs, hormone hypersecretion, time and outcome of surgery, use of chemotherapy and/or radiotherapy in combination with mitotane, duration of mitotane therapy, mitotane dose in g/day (starting dose during the first two months and maintenance dose thereafter). We also evaluated the proportion of patients achieving mitotane plasma levels $\geq$ 14 mg/L during the study period, the median time to first observation of a mitotane plasma level $\geq$ 14 mg/L, adverse effects attributed to mitotane therapy according to the investigator assessment, and the proportion of and reasons for permanent discontinuation of mitotane therapy. The patients included in the study were followed-up until 30 June 2013, in order to obtain more accurate information on recurrence, progression and mortality.

The data were analysed by means of descriptive statistics and are presented as mean $\pm$ standard deviation (SD), median and range of values or proportions (%). For normally distributed continuous variables, differences between subgroups of patients were analysed using unpaired Student *t*-tests, while the Kruskal–Wallis test was used for asymmetrically distributed continuous variables. The Chi^2 test was used to compare categorical variables.

Overall survival (OS) was calculated as the time from diagnosis to death or to the last visit before 30/06/2013, and disease-free