A case report of a TDM-guided optimization of mitotane for a safe and effective long-term treatment

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Abstract

A 43-years old woman was diagnosed an adrenocortical carcinoma (AC) that was excised, whereas two lung metastases were unoperable. Mitotane 6 g/day was started as standard therapy but it was responsible for severe central nervous system (CNS) and gastrointestinal toxicities associated with a 10-kg body weight loss. A therapeutic drug monitoring (TDM) protocol demonstrated that mitotane plasma concentrations (>30 mg/L) exceeded the therapeutic range (14-20 mg/L) and increased even when drug daily dose was reduced by 50%. The increase in drug plasma concentrations was probably due to body slimming. Under continuous TDM control, a reduced mitotane dose (1.5 g/day) was definitively administered and it proved to be tolerable and effective. Indeed, lung metastases were excised and 2 years later there was not evidence of other neoplastic lesions. In conclusion, the adoption of therapeutic mitotane monitoring allowed the treatment of an AC patient with a reduced, tolerable and effective dose.

Keywords: mitotane, therapeutic drug monitoring, dose optimization, toxicity

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Introduction

Mitotane finds its selective use in the treatment of adrenocortical carcinoma (AC), against which the drug is effective alone or in combination with other pharmacological agents (Fassnacht and Allolio, 2009). Indeed, in adjuvant setting, mitotane significantly improves the disease-free survival at the cost of moderate toxicities (Terzolo et al., 2007). In advanced disease, mitotane shows to control disease progression with a median overall survival of 12.0-14.8 months depending on the combination regimen (Fassnacht et al., 2012). Even in that setting, the administration of mitotane may be associated with neurological and gastrointestinal toxicities that may require a decrease in daily dosage or the discontinuation of therapy (Maiter et al., 2016). In the latter case, the patient may lose the therapeutic benefit of drug administration.

Being a highly lipophilic drug, mitotane has a wide tissue distribution and a long terminal half-life, so that the steady state may be achieved after several weeks of therapy (Baudin et al., 2001). Furthermore, clinical studies have demonstrated that the patients may achieve the best therapeutic benefit when minimum plasma concentrations (C_{min}) of the drug are within the range 14-20 mg/L (Terzolo et al., 2007; Kerkhofs et al., 2014). However, the long terminal half-life explains the delay by which every modification in plasma levels occurs after a change in drug dosage, even if the timing of blood withdrawal should be carefully considered because plasma concentrations of mitotane display wide fluctuation after drug intake (Kerkhofs et al., 2014). For all of these reasons, the therapeutic drug monitoring (TDM) may improve the management of AC patients both in adjuvant and palliative settings.

Case presentation

A 43-years old woman referred in our Unit complaining a body weight increase (56 vs 53 Kg), hirsutism, polymenorrhea and menorrhagia, hypertension (range 140-160 mmHg for systolic and 85-100 mmHg for diastolic blood pressure) and headache. The clinical history did not reveal any particular cause; hence, the physician prescribed a estro-progestinic therapy (May 2013) that did not ameliorate the symptoms. At next follow-up visit (November 2013), the examination returned the following data: body weight 56 kg, body mass index 21, persistence of hirsutism and hypertension (150/90 mmHg, 70 bpm), appearance of arm and leg ecchymoses. Laboratory analyses were within normal range, but abdominal echography revealed a suprarenal mass of 6 cm in diameter. Computerized tomography (CT) scan showed the presence of the mass (55x48x60 mm) together with two lung masses (17x11 mm and 8x8 mm), a finding confirmed by ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) on December 2nd, 2013). Hormonal evaluation showed the presence of a highly vascularised suprarenal mass producing sexual hormones (dihydroepiandrostenedione 334 μg/dL, estradiol 519 pg/mL, estrone >2000 pg/mL), mineralcorticoids (aldosterone 32 ng/dL, plasma renin activity 1.2 ng/ml/h) and free urine cortisol (38.7 μg/dL). The patient underwent surgery and the neoplasm was excised (December 10th, 2013). Histological diagnosis confirmed the adrenocortical carcinoma (stage IV UICC/WHO 2004 and ENSAT 2008) with Ki-67 proliferation index of 15%.

As per guidelines, mitotane (Lysodren®) 3 g/day was started on January 4th, 2014 and dose was increase up to achieve a daily dose of 6 g in the next 6 days. This treatment was associated with cortisol replacement therapy (hydrocortison acetate 37.5 mg/day) to maintain an adequate hemodynamic and electrolytic balance.

Methods

Informed consent

Informed and written consent was obtained from the patient.

Evaluation of treatment efficacy and tolerability

The efficacy of mitotane was evaluated by CT scan and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) as per guidelines, while toxic effects induced by mitotane were assessed on a monthly base and scored according to the Common Toxicity Criteria-Adverse Events vers. 4.03.

Measurement of plasma concentrations of mitotane

Blood samples were obtained early in the morning before drug intake in order to minimize errors (Kerkhofs et al., 2014). They were collected in tubes containing lithium-heparin and sent immediately to the laboratory for processing. Samples were centrifuged at 5,000 rpm for 10 min and resulting plasma was stored at +4 °C until the measurement was performed within the next hour. Plasma concentrations of mitotane were assessed by a validated high-performance liquid chromatography method with UV detection as previously described (Francia et al., 2006).

Results

After three weeks of treatment, moderate-to-severe toxicities occurred, mainly related to central nervous system (CNS) (confusion, absences, somnolence) and gastrointestinal symptoms (nausea, diarrhea, anorexia) that were accompanied by a decrease in body weight (43 Kg). Because of the persistent CNS symptoms, mitotane dose was reduced to 4.5 g/day (February 2nd) then a TDM protocol was started to check whether drug

plasma levels were within the therapeutic range. Results of TDM revealed a C_{min} value of 30.7 mg/L (February 25th) and the dose was promptly reduced to 3 g/day (Figure 1). One month later (March 20th), the next measurement of drug plasma concentrations gave a result of 36.2 mg/L that immediately required a further decrease in mitotane dose to 1.5 g/day. At that time neurological symptoms improved, whereas nausea and diarrhea still persisted. However, despite the decrease in daily dose, mitotane C_{min} value was still higher than the therapeutic range (33.0 mg/L on April 29th), so that physicians reduced the dose to 1 g/day (May 7th). Toxic effects progressively improved, despite a body weight reduction, mild diarrhea and muscular stiffness were still present. CT scan confirmed disease stabilization of the lung metastases without any further sign of the disease, hence the daily dose of 1 g was maintained. On June 12th, for the first time since the beginning of chemotherapy, mitotane plasma concentration was 20 mg/L. At that follow-up visit, the patient referred a further improvement in symptoms, and physical examination showed a blood pressure of 120/70 mmHg, absence of postural hypothension, normal results from lab analyses except for a normocytic anemia. Hirsutism, polymenorrhea and menorrhagia disappeared.

On September 11th, C_{min} value of mitotane accounted for 7.7 mg/L, well below the therapeutic range. Therefore, the dose was increased to 1.5 g/day, and a closer monitoring was performed on December 2014, when C_{min} value was 11.7 mg/L. On January 2015 the two little lung metastases were surgically removed and plasma concentrations of mitotane were measured over the next two years, ranging from 9.4 mg/L (December 2014) up to 14.7 mg/L (April 2016, Figure 1). During that time interval mitotane dose was maintained at 1.5 g/day. At this regimen the drug was well tolerated with occasional tiredness and tachycardia. Blood pressure was normal (120/80 mmHg), body weight recovered (58 Kg) and gastrointestinal and neurological

symptoms disappeared. CT scans (January and July 2016) did not show recurrence of disease or metastases. On December 2016, mitotane plasma concentration was 9.4 mg/L, while 5 months later (May 2017) ^{18}F-FDG PET did not show any abnormal uptake of the radiotracer.

Discussion

The present case report supports TDM protocols for mitotane in order to optimize the dose of the drug in the presence of toxicities, and to confirm dose appropriateness when changes in dosage were adopted. Indeed, mitotane was able to arrest disease progression even at a reduced but tolerable dose, as previously demonstrated (Terzolo et al., 2000). More interestingly, during the first four months of treatment, plasma concentrations of mitotane not only did not reduce, but they even increased despite the tapering daily dose. That surprising finding could be explained by the extensive accumulation of mitotane, a highly lipophilic drug, in several tissues, such as adipose tissue (Baudin et al., 2001). As a consequence, the rapid and evident body weight loss (10 kg, approximately 18% of initial body weight at the beginning of chemotherapy) could be responsible for the release of the mitotane stored within tissues, making it newly available in plasma for redistribution processes. In the absence of TDM, it is likely that the patient had to discontinue mitotane intake due to intolerable toxicity at standard doses. On the contrary, the measurement of drug plasma concentrations demonstrated that a 75% dose reduction was not only tolerable in long term treatment, but also effective. Indeed, it was possible to excise the two lung metastases without the evidence of new lesions in the next two years of follow-up.

To conclude, the present case report demonstrates the usefulness of mitotane TDM to individualize drug dosage, despite the need for appropriate instrumentation (i.e., liquid chromatography apparatus with suitable detectors) may be a hurdle for the diffusion of

such an activity. However, TDM benefits for the patients and the caregivers greatly outweigh the disadvantages.

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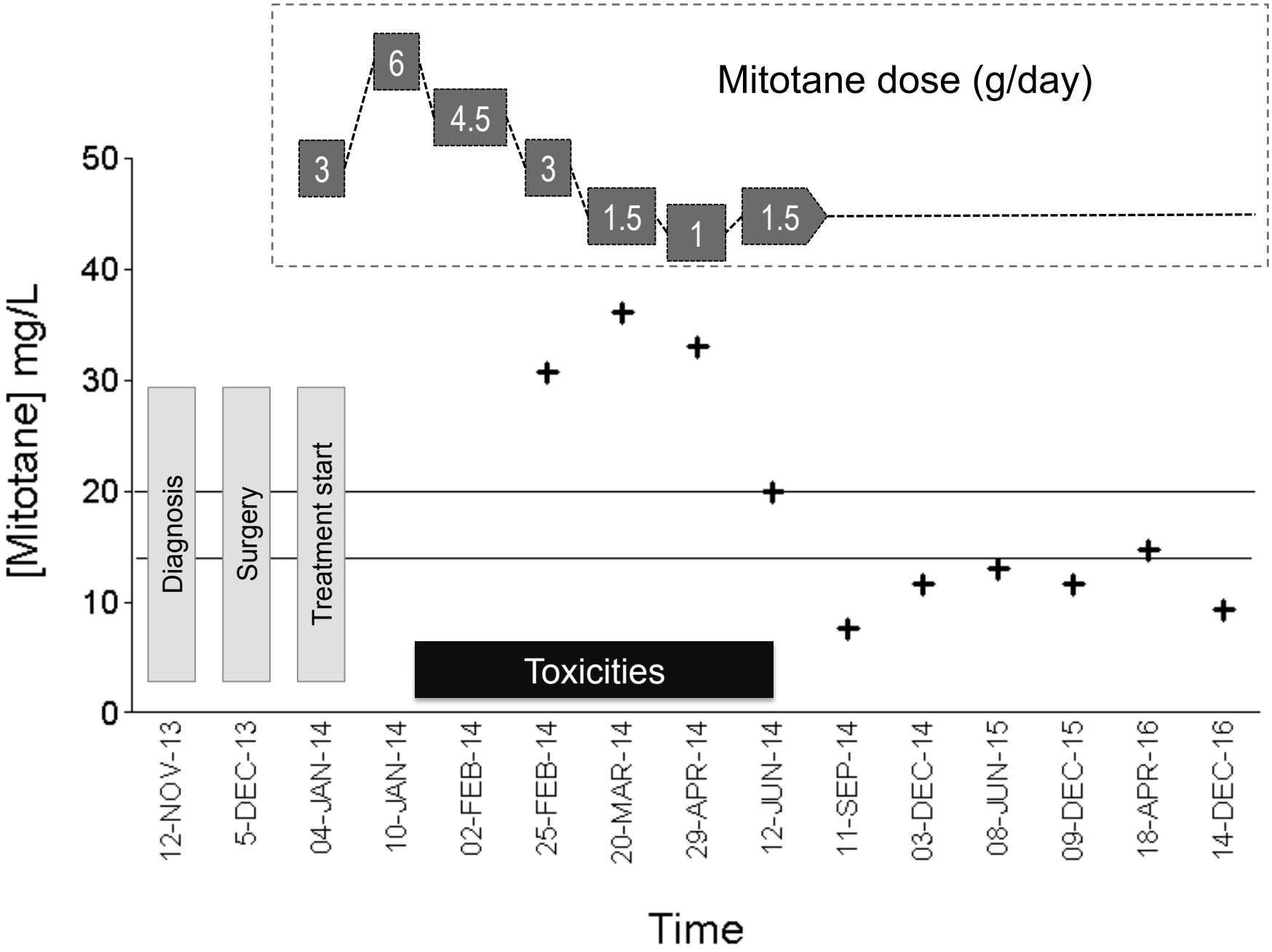
Figure

Figure 1. Plasma concentrations of mitotane and its daily dose over time. Treatment started on January 4th, 2014 and daily dose increased from 3 up to 6 g/day in the first 6 days of therapy as per guidelines. After February 2nd, 2014, the daily dose of mitotane was reduced for the toxic effects of treatment and because high mitotane plasma concentrations, until treatment was well tolerated at doses of 1.5 g/day. The black rectangle represents the duration of toxic effects. Numbers in grey boxes are the daily doses of mitotane, while black crosses represent the measured plasma concentrations of the drug plotted within the graph.


Mitotane dose (g/day)
3
6
4.5
3
1.5
1
1.5
[Mitotane] mg/L
50
40
30
20
10
0
Diagnosis
Surgery
Treatment start
Toxicities
12-NOV-13
5-DEC-13
04-JAN-14
10-JAN-14
02-FEB-14
25-FEB-14
20-MAR-14
29-APR-14
12-JUN-14
11-SEP-14
03-DEC-14
08-JUN-15
09-DEC-15
18-APR-16
14-DEC-16
Time