High-Dose Mitotane-Induced Encephalopathy in the Treatment of Adrenocortical Carcinoma

We read with great interest the article of Reidy-Lagunes et al. in which the authors evaluated progression of disease and treatment-induced toxicity among a cohort of 36 patients treated with mitotane for metastatic adrenal cortical carcinoma (ACC) [1]. As mentioned by the authors and reported in many retrospective studies, the difficulty of this treatment is the probable requirement of high doses of mitotane to maintain high blood levels within a narrow therapeutic range of concentrations (14–20 mg/L) to induce a beneficial outcome in patients with ACC [2–5]. Indeed, if starting high-dose mitotane monotherapy (4–6 g per day) seemed to induce prolonged survival in patients without significant increase in the rate of toxicity in comparison with low-dose regimen (2–3 g per day) [6, 7], mitotane is not exempt from toxicity. In addition to the toxicities reported by Reidy-Lagunes et al., we report herein a case of mitotane-induced encephalopathy.

A 25-year-old white female patient treated with high dose of mitotane (4 g per day) for ACC presented toxicity signs such as adrenal insufficiency and digestive and neurological toxicity (nausea, vomiting, anorexia, dizziness, memory troubles) that were similar to those reported by Reidy-Lagunes et al. and generally described by Reidy-Lagunes et al., Daffara et al., and Maiter et al. [1, 2, 8]. After 32 weeks of treatment, while a close monitoring and decrease of mitotane dose was already initiated due to an upper-limit concentration of mitotane (Fig. 1), neurological troubles (attention deficit disorder, memory loss, mental depression) worsened. Mitotane treatment was discontinued at 42 weeks of treatment and a performed electroencephalography suggested metabolic encephalopathy. Concomitantly, the determination of mitotane plasma concentration found a concentration of 47.8 mg/L and confirmed a mitotane overdose despite the decrease of its dosage 11 weeks before. Finally, the outcome was favorable after hospitalization in an intensive care unit. One year after tumor resection, no recurrence of malignancy was observed.

Although symptoms of neurotoxicity have already been reported, the specific entity of encephalopathy has been rarely described. Indeed, to the best of our knowledge, only Goto et al. reported a case of encephalopathy in a 4-year-old boy with a high-dose mitotane treatment for ACC [9]. Furthermore, a query in the French national pharmacovigilance database from 2004—the date of mitotane commercialization in France—to 2016 found only 14 cases of neurological adverse effects probably related to mitotane, including drowsiness, asthenia, memory disorders, confusion, concentration troubles, headaches, and space-time disorientations, but no case of encephalopathy [10]. It appears that encephalopathy can be a rare but severe adverse event preferentially encountered in high-dose mitotane treatment. A close therapeutic drug monitoring should be performed in case of signs of neurological toxicity to evaluate the exposure of the patient to mitotane. Finally, the decision of mitotane discontinuation should be considered from the early signs of neurotoxicity or in the presence of elevated mitotane blood concentration because mitotane presents a very long terminal half-life (several weeks to several months), leading to an important delay between the decision of treatment discontinuation and the effective decrease of exposure. This case was reported to our Regional Center of Pharmacovigilance.

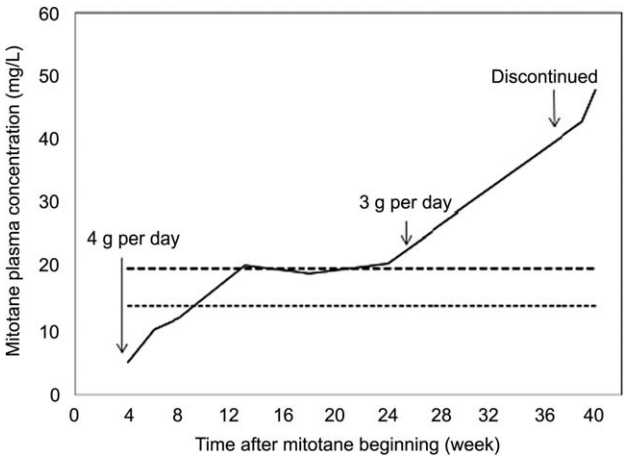

Figure 1. Therapeutic drug monitoring of mitotane during the whole period of treatment. Vertical arrows show daily dose of mitotane and modification of dosage. Bold and faint dotted lines correspond to the upper and lower therapeutic ranges, respectively.

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Disclosures

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