Influence of the CYP2B6 polymorphism on the pharmacokinetics of mitotane.

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Mitotane is the reference agent for treatment of adrenocortical carcinoma (ACC), a rare tumor with a dismal prognosis and a 5-year survival of less than 50%. Mitotane antitumor efficacy is observed with plasma concentrations >14 mg/l while severe toxicity is associated with concentrations >20 mg/l. Mitotane levels correlate grossly with the assumed dose, but other factors contribute to attainment of blood levels. Mitotane metabolism is mainly mediated by CYP2B1, 3A1, 2B6, and 3A4. Our aim was to assess the potential impact of genetic determinants on mitotane pharmacokinetics and on patient response.

We performed a retrospective analysis on 66 ACC patients treated with mitotane. Drug plasma levels were determined by a HPLC-UV validated metod (De Francia, 2006); pharmacogenetic analysis was performed with RT-PCR on CYP2B6_516G>T, ABCB1_1236C>T, ABCB1_2677G>T and ABCB1_3435C>T.

Patients with wild type CYP2B6_516 had significantly lower mitotane levels than those with mutated gene after 3 and 6 months of treatment (p=0.03 and p=0.05, respectively). Afterwards, difference was not longer significant due to dose adjustments based on mitotane levels. In univariate analysis there was no difference in clinical outcome between the 2 groups. Patients with wild type ABCB1_1236 and ABCB1_2677 showed higher mitotane levels at 6 months of therapy (p=0.01 and p=0.04, respectively). ABCB1_3435 had no influence on mitotane levels.

In conclusion, we identified a genetic profile predictive of mitotane levels that may be potentially useful to select the start-up mitotane regimen (low-dose vs. high-dose).

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