CLINICAL AND BIOCHEMICAL EFFECTS OF ADJUVANT MITOTANE TREATMENT IN PATIENTS WITH ADRENOCORTICAL CANCER (ACC).

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Sixteen patients (seven men, nine women: median age 37 years, range 22-58) radically resected for ACC were treated with adjuvant mitotane and prospectically followed from 2000 to 2006. Stage of ACC was: 1 stage I, 11 stage II, 4 stage III (according to Mc Farlane-Sullivan); Weiss score: 6 (range 3-9); Ki67%: 22,5 (range 4-67). Twelve patients had functional tumors: eight with Cushing's Syndrome, one with hyperaldosteronism, three with androgen secretion. Median duration of treatment was 23,5 months (range 6-84); thirteen patients are currently on mitotane, two died and one interrupted treatment after five years. All patients were treated with a middle-low dose regime (till 3-4 g/die) and underwent monitoring of plasma mitotane level every three months. None of the patients interrupted mitotane definitively for side effects and all patients reached the therapeutic levels after a median time of three months (range 1-6). At the last follow up, 6/16 (37%) patients have relapsed, fourteen patients are still alive. Hyperprolactinemia was observed in 40% of men and 45% of women; 85% of men become partially hypogonadic with reduction of free testosterone greater than total testosterone. Central hypothyroidism developed in eleven patients, while four patients, already on thyroxine, required dose increment. Fourteen patients developed overt hypoadrenalism after a median time of three months, eight patients developed hypoaldosteronism. Total cholesterol level were slightly enhanced with overt increase of HDL and weak increase of LDL, while triglicerides were normal. Reduction of folate level and consequent increase of homocysteine were also observed. We also observed that mitotane levels were inversely correlated with cortisol ($p=0.01$), FT4 levels ($p=0.05$) and free testosterone ($p=0.008$), while they were positively correlated with HDL levels ($p=0.006$) and with LH levels ($p=0.0004$). In conclusion, a middle-low dose regime of adjuvant mitotane is well tolerated and able to reach the therapeutic interval. Adequate supplementation of adrenal and sex steroid and thyroid hormones is necessary. Some effects of mitotane may be ascribed to either adrenolytic or estrogen-like actions of the drug.