Tailored hormonal therapy in secretory adrenocortical cancer

Mitotane is often considered the front-line hormonal therapy of adrenocortical carcinoma (ACC). An illustrative case concerning this issue and the rationale to ponder other alternatives is reported. A 69 year-old woman, diagnosed with ACC was admitted with hypertensive crisis, supraventricular tachycardia, congestive heart-failure, diarrhoea and rhabdomyolysis. Two years earlier, she had undergone suprarenalectomy because of a unilateral 8-cm adrenal mass with raised aldosterone (525 pg/ml), consistent with a diagnosis of Conn syndrome. After surgery she did not receive any adjuvant treatment and remained asymptomatic, while hormonal parameters returned to normality. Locorregional and lung relapse was observed after 8 months of disease-free survival. Mitotane 3 g daily was started, with 3 months of radiological stabilization. At progression she received chemotherapy with cisplatin, doxorubicin, etoposide and mitotane. Eight cycles were administered until September 2006, with partial response and symptomatic improvement, but NCI-grade 2 nausea and neurological toxicity. Elevated aldosterone (567 pg/ml) and hypokalemia (K 2.2 mEq/l), normal cortisol and raised aldosterone (269 pg/ml), Mitotane was stopped and high-dose spironolactone 400 mg/d, ketoconazole 1 g daily, hydrocortisone, captopril and potassium supplements were prescribed. In a few days aldosterone increased to 900 pg/ml, while cortisol remained stable. Nevertheless, the patient improved gradually, potassium normalized and blood pressure stabilized. Eight months symptomatic improvement and excellent palliation were achieved with these drugs. Three months later CT revealed progressive locoregional disease, and aldosterone raised to 2000 pg/ml, without apparent symptomatic changes.

ACC is an uncommon neoplasia with an interesting pathogenic background. Half of these tumours are secretory. Cushing syndrome and virilization occurs in 60 and 35% of functioning tumours respectively, but only 2–7% of patients develop hyperaldosteronism, commonly coexisting with the previous syndromes.

Mitotane achieves a radiological response in one-third of patients and reduces hormonal release in 75% of cases [1] but survival is not affected, and toxicity is prominent. Furthermore, mitotane preferably damages the zona fasciculata and reticularis of the adrenal cortex, relatively sparing aldosterone release in the zona glomerulosa [1]. The effect of mitotane has been reported to be neutralized by spironolactone, and simultaneous administration is unadvised [1]. Ketoconazole inhibits 11β-hidroxilase and desmolase, blocking the synthesis of both aldosterone and cortisol. Anecdotal evidence suggested that ketoconazole was able to induce objective tumour regression [2]; however, this hypothesis could not be confirmed by others [3]. In our case, 3 months after ketoconazole, CT revealed progressive disease with a parallel increase in aldosterone. Spironolactone is a non-competitive inhibitor, and loss of efficacy is expected with increasing aldosterone. As palliation remains the mainstay of therapy, we propose to consider a tailored hormonal strategy: if aldosterone secretion becomes relevant, spironolactone (or epleronone) should be considered the drug of choice. Discontinuing mitotane if previously prescribed is advisable in this setting. However, if aldosterone is very high or competitive phenomena with a mineral-corticoid inhibitor is suspected, adjuvant treatment with ketoconazole or aminoglutethimide could be considered. If Cushing syndrome is predominant, mitotane and ketoconazole (and also aminoglutethimide as an adjuvant) are valid options. Finasteride, cyproterone or flutamide are effective in case of virilization.

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