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Adding metyrapone to chemotherapy plus mitotane for Cushing's syndrome due to advanced adrenocortical carcinoma.

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine tumor that is actively secreting in approximately 50% of adult patients. Cushing's syndrome is the most commonly associated endocrine disorder [1] that negatively influences the outcome of ACC patients, due to cortisol-related comorbidities [2] and the immunosuppressive effects of cortisol excess that may promote tumor progression [3]. The management of ACC patients is challenging and demanding because physicians have to deal with either oncological or endocrinological issues [4].

Currently, the standard systemic treatment for advanced ACC patients not amenable to surgery with radical intent is mitotane, administered either alone or in combination with etoposide, doxorubicin and cisplatin (EDP-M scheme) [1]. Mitotane exerts both adrenolytic and cytotoxic activities [5] and has a narrow therapeutic index defined by circulating levels of the drug between 14 mg/L and 20 mg/L [6]. These concentrations have been associated with drug activity and are usually obtained after several weeks to months of treatment [7]. A slow onset of mitotane activity is a main limitation also for the management of Cushing's syndrome, which needs to be treated promptly not only to ensure a rapid correction of the metabolic complications that may be life-threatening when cortisol excess is severe, but also to improve patient well being aiming to make feasible antineoplastic therapies. Thus, there is a need to associate drugs able to reduce serum cortisol levels in an effective and fast way.

Metyrapone (Cormeto, HRA Paris) is an adrenolytic molecule targeting the 11-beta-hydroxylase that is currently used to treat Cushing's syndrome of different etiologies [8]. The drug inhibits the conversion of 11-deoxycortisol into cortisol obtaining the reduction of cortisol synthesis within 2 hours after the first drug administration [9].

Metyrapone metabolism and elimination are not altered by concomitant mitotane, which is known to be a strong hepatic enzyme inducer [10]. Indeed, metyrapone is mainly metabolized by hepatic reduction; metyrapone and reduced metyrapone are then conjugated to the corresponding

glucuronides and nearly 40% of the administered dose is excreted in the urine within 2 days [11]. There is limited evidence from isolated case reports or small case series that metyrapone is effective in the management of hypercortisolism induced by ACC, but the drug administered alone did not show to have an effective antineoplastic action [8;12].

We reported herein the feasibility and activity of the combination of metyrapone with EDP-M in three consecutive advanced ACC patients with Cushing's syndrome.

Patients and methods

From January to June 2016, 3 consecutive male patients with newly diagnosed ACC and full-blown Cushing's syndrome were referred to the Medical Oncology Unit of ASST Spedali Civili of Brescia, Italy. Two patients had metastatic disease (lung and supra-clavicular lymphnode involvement, respectively), one had inoperable locally advanced disease. All patients presented with poor general conditions, elevated levels of serum and urinary cortisol and severe hypokalemia (Table 1). A complete hormonal evaluation was performed at baseline and immediately after the patients received EDP-M (etoposide 100 mg/m² iv. on days 2, 3 and 4, doxorubicin 40 mg/m² iv. on day 1, cisplatin 40 mg/m² iv. on days 3 and 4, plus mitotane at an initial dose of 1 g daily, with progressive increase up to 6 g daily, or the maximum tolerated dose). The chemotherapy regimen was given in association with metyrapone at the initial daily dose of 250 mg/tid per os [8;9] and, at each cycle, patients received pegylated granulocyte colony stimulating factor (G-CSF) for chemotherapy-induced neutropenia primary prophylaxis.

Results

During the first 4 weeks of treatment, the patients' conditions markedly improved and urinary free cortisol (UFC) dropped significantly, while the reduction of serum cortisol was less evident (Table 1). The metyrapone dose was gradually tapered over time according to clinical improvement of the Cushing's syndrome. The drug was then discontinued after 16 weeks in patient 1, 12 weeks in patient

2 and 8 weeks in patient 3. None of the patients received steroid replacement over the 12 weeks of therapy considered in this case series. Disease restaging performed at week 12 showed a partial response and a minor response (< 30% reduction not qualifying for a partial response according to the RECIST criteria) in patient 3 and 2, respectively (Table 1). Both patients underwent surgery and are currently disease free at 9 and 7 months of follow-up (patient 3 and 2, respectively). The patient 1 developed disease progression after three months and was subsequently referred to a palliative-care program, due to the deterioration of his general conditions.

During the EDP-M-metyrapone combination regimen, the major toxicities observed were asthenia and nausea. Two patients (patient 1 and 2) received red blood cell transfusion for severe grade anemia. None of the patients developed neutropenia, due to the adoption of primary prophylaxis. Patient 1 transiently interrupted both metyrapone and mitotane for 6 days, due to the persistence of severe nausea and asthenia after chemotherapy administration.

Discussion

Metyrapone is an effective drug to manage Cushing's syndrome of either origin [8]. The drug has been also employed in the management Cushing's syndrome associated with ACC either administered alone or in association with other inhibitors of steroidogenesis [8], or chemotherapy [13;14]. At the best of our knowledge, there are no published data on feasibility and activity of this drug in association with the current standard therapy for advanced ACC, EDP plus mitotane.

Due to its pharmacokinetic characteristics, metyrapone displays a good safety profile with minor drug-to-drug interactions [15]. No interactions have been reported with mitotane and/or EDP [11].

In the present case series, the addition of metyrapone to EDP-M led to a rapid resolution of symptoms and signs of Cushing's syndrome and a significant improvement of the patient general conditions. The control of cortisol hypersecretion was obtained in few days in patient 2; the rapid increase of mitotane serum levels in this patient may have likely contributed to the effect. We would like to underline this finding, because EDP-M requires several weeks to attain a control of hypercortisolism. Metyrapone was well tolerated and did not increase the toxicity of the EDP-M regimen, since we did not observe unexpected toxicities [16;17]. The three patients included in this report completed the chemotherapy

plan and adding metyrapone to the EDP-M regimen did not alter EDP-M efficacy in terms of tumor control, since 2 patients obtained a disease response and underwent radical surgery.

In conclusion, this case series shows that the combination of EDP-M with metyrapone is effective and leads to a rapid control of Cushing's syndrome induced by cortisol-secreting ACC. This combination may represent a rapid, effective and well-tolerated treatment of excess hormone secretion in advanced ACC. Our results, although interesting, need validation in a prospective study.

Disclosures

Conflict of Interest: The authors declare that they have no conflict of interest.

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Table 1 - Clinical features, laboratory assays and hormonal evaluations of three patients with severe Cushing ACC at baseline and after 4, 8 and 12 weeks of treatment with metyrapone, EDP and mitotane.

		Patient 1				Patient 2				
	Reference range	Baseline	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12	Baseline
Age (years)		66				53				
Disease stage		IV				IV				
PS ECOG		1	1	2	2	3	3	2	2	
Secretory status		Cortisol				Cortisol				Cortisol
Mitotane daily dose (mg)		3000	discontinued	3000	3000	3000	3000	3000	3000	3000
Metyrapone daily dose (mg)		750	discontinued	500	250	750	500	250	250	750
Mitotane serum level (µg/dL)	14 - 20				6				13	
Serum cortisol	5 - 20 (morning)	36	24	21	17	29	19	8	6	29

(µg/dL)	values)									
UFC (µg/24h)	10 - 116	334	114	n.a.	87	136	13	13	n.a.	>
ACTH (pg/mL)	< 46	<5	12	9	< 5	<5	<5	<5	<5	<
DHEAS (ng/mL)	0,80-5,6	13	12	4	n.a.	0	0	< 0,15	<0,15	
Weight Kg (BMI)		70 (26,53)	57 (21,45)	60 (22,58)	57,5 (21,64)	116 (39,21)	105 (35,49)	105 (35,49)	107 (36,17)	(23
Central obesity		yes	no	no	no	yes	yes	yes	yes	y
Glucose (mg/dL)	70-100	77	72	75	110	124	89	79	90	1
K+ (mEq/L)	3,3-4,7	3	5	4	4	3	4	4	4	
EDP major toxicities										
	Nausea/Vomitin g		G3	G3	G2		G0	G0	G0	
	Astheni a		G3	G3	G3		G2	G2	G1	
	Neutrop enia		Primary prophylaxis				Primary prophylaxis			
	Anemia		G3	G1	G1		G3	G1	G1	
	Thromb ocytope nia		G2	G1	G1		G0	G0	G0	
Disease response					PD				MR	

Disease stage according to ENSAT (European Network for the Study of Adrenal Tumors); PS ECOG: Eastern Cooperative Oncology free cortisol; ACTH: adrenocorticotrophic hormone; DHEAS: dehydroepiandrosterone; BMI: Body Mass Index; K+: serum potassium; no: absence of the characteristic; EDP: etoposide, doxorubicin and cisplatin (chemotherapy scheme); n.a.: not available; Toxicity Criteria for Adverse Event ver. 4.03 (2010): G1 mild, G2 moderate, G3 severe, G4 life-threatening, G5 death; Disease response Criteria in Solid Tumors) ver. 1.1: CR complete response: disappearance of all target lesions, PR partial response: at least a 30% reduction in the sum of diameters of target lesions, taking as reference the baseline sum diameters, MR/SD minimal response/stable disease: neither sufficient shrinkage to qualify for PR, nor sufficient increase in the sum of diameters of target lesions to qualify for PD, PD progressive disease: at least 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an appearance of one or more new lesions is also considered progression)