Early progression under mitotane and polychemotherapy does not mean failure in adrenocortical carcinoma patient

Une progression précoce sous mitotane et polychimiothérapie n’est pas synonyme d’écchec chez les patients porteurs de corticosurréalome

1. Case description

A 52-year-old female underwent surgery in March 2009 for a localized non-secretory adrenocortical carcinoma (ACC) of 17 cm. A Weiss score of 9 with a mitotic rate of more than 5/50HPF and a Ki67 of 10% were reported at pathology. Baseline imaging work-up showed pulmonary micronodules, hepatic and bones metastases and peritoneal carcinomatosis (Fig. 1A). Mitotane therapy was started in April 2009, with carboplatin-etoposide (MPE) because of pejorative prognostic factors. Response to treatment was evaluated every 2 months with CT based on RECIST 1.0 criteria and mitotane plasma level was monitored monthly (Fig. 1). The therapeutic window of mitotane plasma level was reached with a daily dose of 3 g/day 4 months after treatment initiation. Furthermore, a peak of 20 mg/L was reached twice on month 4 (19.2 mg/L) and on month 5 (20.6 mg/L). Along with that mitotane levels, a progressive disease was found until month 6 evaluation (Fig. 1B–D). Imaging work-up performed at month 8 after 6 cycles of EP and 2 cycles of carboplatin-etoposide found a stable disease and only mitotane was continued and decreased due to side effects at maximum tolerated dose. Locoregional approaches to treat the symptomatic bones metastasis were performed at month 10 (cimentoporty, osteosynthesis and cryotherapy). A tumor response (hepatic partial response and pulmonary complete response) was observed for the first time 10 months after MEP initiation, 2 months after the end of carboplatin-etoposide and 6 months after mitotane peak was reached (Fig. 1F). Under mitotane alone, tumor response lasted 21 months after treatment initiation (Fig. 1G and H). At this time, because of progression in hepatic targets concomitant with a plasma mitotane level above 14 mg/L, radiofrequency was performed, making RECIST criteria not usable anymore on the liver while bone metastases were all treated with loco-regional approaches. Since 2010, the disease of this patient is still under control with the same strategy (locoregional approaches and mitotane) and a survival of more than 6 years after initial stage IV diagnosis.

2. Discussion

Adrenocortical carcinoma (ACC) prognosis is characterized by a 5-year survival of less than 15% at metastatic stage. Mitotane (o,p’DDD), an insecticide-derivative, is the only drug approved in advanced ACC either as monotherapy or combined polychemotherapy according to prognostic features [1]. Although targeting 14 to 20 mg/L, therapeutic plasma level window of mitotane is recommended [2], the time at which mitotane antitumor efficacy should be evaluated remains ill-defined. As a consequence, resistance to mitotane therapy is still not precisely defined and a significant number of ACC patients remains on mitotane therapy lifelong hampering proper evaluation of new therapeutic options. On the other hand, mitotane might be stopped too early in patients because of progression who could benefit from this therapy for prolonged period of time. We report here the case of a patient presenting with a stage IV ACC whose prolonged partial response was evidenced 6 months after mitotane level peak reached 14 mg/L after several tumor progressive status evaluations.

In medical oncology, demonstration of tumor progression challenges the continuation of the ongoing option. This clinical case illustrates a stage-IV bad prognostic ACC patient according the mENSAT-GRAS criteria [3], managed with polychemotherapy including mitotane, who turned into a long-term survivor thanks to a maintained partial response. Because partial response was first obtained at month 10, 2 months after EP regimen withdrawal and maintained for more than 6 years, we classified that response as due to mitotane therapy. However, we cannot eliminate a role of combined cytotoxic chemotherapy. Indeed, delayed response has not been described with cytotoxic chemotherapy alone whereas delayed antitumor activity is a well-known characteristic of mitotane, best demonstrated by the delayed time of several months needed to reach plasma therapeutic level in ACC patients [4]. Although, higher response rate and survival has been reported when plasma mitotane reached 14 mg/L, the kinetic of tumor response according to plasma mitotane level curve has never been reported. This case allows us to raise the hypothesis that the antitumor evaluation of mitotane therapy should be evaluated after the peak of plasma mitotane has been reached. In this case, plasma mitotane levels of 20 mg/L have been reached two times prior the demonstration of a long lasting partial response. From that date forth, plasma mitotane level was retrieved higher that 10, 14 or 20 mg/L out of 3, 3 or 1 measurements before the first demonstration of progression was evidenced. Recent literature on mitotane has suggested that both very high plasma mitotane levels above 20 mg/L and maintenance of therapeutic level were associated with better response rates and recurrence free survival [5,6]. In oncology, complete responses to chemotherapy or targeted agents are rare and various mechanisms of resistance have been proposed to explain reprogression. Targeting microenvironment rather than the tumor itself has been proposed to escape redundant pathway mechanisms of resistance. Antiangiogenic agents or immunotherapy have emerged as a promising application of such paradigm and unusual features of pseudoprogression have been described [7]. Mitotane has unique metabolic properties. Indeed, due to its lipophilic nature, plasma mitotane has been shown to mainly reflect lipoprotein binding [4]. In addition, recent publication has favored a direct intracellular mitochondrial targeting [8,9]. Finally, alteration of intracellular lipid profile as characterized by an increase in free cholesterol has been demonstrated and sterol O-acyltransferase 1 (SOAT1) proposed as the main target [10]. In the light of these observations, we hypothesize that the unique profile of delayed tumor response reported in this patient may resemble pseudo progression described in patients treated with immunotherapy.
and, may reflect profound lipid metabolism targeting alteration induced by mitotane in the plasma and tumor cells of ACC patients. Mitotane could be maintained as long as it is well tolerated or effective but discussed in patients who cannot reach 8–10 mg [6].

In conclusion, we suggest that antitumor evaluation of mitotane therapy should be performed after at least one peak of mitotane. Retrospective and prospective studies are ongoing to confirm that result and the role of combined cytotoxic chemotherapy. Metabolomic targeting is proposed as an explanation of this unique profile of tumor response kinetic.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


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