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MINI REVIEW

Management of adjuvant mitotane therapy following resection of adrenal cancer

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Abstract Whenever adrenal cancer (ACC) is completely removed we should face the dilemma to treat by means of adjuvant therapy or not. In our opinion, adjuvant mitotane is the preferable approach in most cases because the majority of patients following radical removal of an ACC have an elevated risk of recurrence. A better understanding of factors that influence prognosis and response to treatment will help in stratifying patients according to their probability of benefiting from adjuvant mitotane, with the aim of sparing unnecessary toxicity to patients who are likely unresponsive. However, until significant advancements take place, we have to deal with uncertainty using our best clinical judgement and personal experience in the clinical decision process. In the present paper, we present the current evidence on adjuvant mitotane treatment and describe the management strategies of patients with ACC after complete surgical resection. We acknowledge the limit that most recommendations are based on personal experience rather than solid evidence.

Keywords Adjuvant treatment · Adrenal cancer · Mitotane · Recurrence-free survival

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Aim of the review

To present the current evidence on adjuvant mitotane treatment and describe the management strategies of patients with adrenal cancer after complete surgical resection. We acknowledge the limit that most recommendations are based on personal experience rather than solid evidence.

Adjuvant mitotane treatment: what is the evidence?

Adrenal cancer (ACC) is a rare tumor characterized by a poor prognosis since 5-year survival rate after diagnosis is less than 40 % [1–3]. The main factor influencing prognosis is the possibility of a radical surgery; however, most of the tumors which undergo a complete, margin-free resection will recur, often with distant metastases [4–8]. This observation has prompted to consider systemic therapy following the removal of ACC; mitotane, a parent compound of the insecticide DDT, has been the drug most frequently employed in an adjuvant setting [1–3, 5–8].

It is known from many years that administration of mitotane was able to destroy the adrenal glands in animal models [9] and to inhibit different enzymatic steps of adrenal steroidogenesis [10]. It is generally thought that mitotane cytotoxicity is mediated through binding of the reactive acyl-chloride to mitochondrial proteins and subsequent oxidative damage through generation of free radicals [10, 11]. It has also been demonstrated that mitotane is able to sensitize H295R and SW-13 ACC cells to ionizing radiations by attenuating DNA repair and interfering with cell proliferation [12]. These findings suggest that mitotane, in addition to the assumed binding to proteins and phospholipids, may interact also with DNA. The

activity of mitotane depends on metabolic transformation of the drug in the mitochondria catalyzed by a P-450 enzyme, giving adrenal selectivity [13].

Mitotane has a narrow therapeutic index and the potential to cause significant toxicity [3, 6, 7]; thus, it is not an ideal drug to treat patients free of disease. This concept coupled with a limited evidence of efficacy in the literature published since recently [5–8, 13–17] made adjunctive treatment with mitotane progressively less appealing. As a matter of fact, no recommendation in favor or against adjuvant treatment was formulated at a consensus conference on ACC held at Ann Arbor in 2003 [18].

In 2007, we published a retrospective analysis involving a large cohort of patients with ACC, followed at different institutions in Italy and Germany, which challenged this view [19]. In that study, adjuvant mitotane was given to 47 Italian patients after radical surgery, and recurrence-free survival in these patients was compared with that of two independent groups of 55 Italian and 75 German patients whose surgical procedures were not followed by mitotane treatment. Recurrence-free survival (the primary outcome of the study) was significantly prolonged in the mitotane group, while the patients who were left untreated after radical resection of ACC had a significantly higher recurrence rate. Multivariate analysis confirmed that mitotane treatment gave a significant advantage for recurrence-free survival and also overall survival after adjusting for an imbalance of prognostic factors among the different groups [19]. An important finding of the study was that a favorable effect was achieved with low doses (1–5 g per day), a possible explanation for the acceptable adverse event rate [13]. Conversely, severe and disabling toxicity was observed in the previous series employing high doses of mitotane [6].

Following publication of our study, Bertherat et al. [20] reported that in a cohort of 166 patients, mitotane use following complete tumor removal was not associated with any improvement in disease-free survival. Since mitotane was given to only half of the patients referred to the Authors' institution a selection bias may be anticipated, implying that patients with unfavorable prognostic factors were selected for adjuvant mitotane treatment. This is a major difference with our study, in which the choice to recommend mitotane was made according to a predefined center policy irrespective of patient or tumor characteristics [19]. The predefined treatment assignment and the inclusion of well-matched control groups were considered to be the major advantages of our study as compared with other studies that had less clear treatment assignments and often used historical controls or no controls at all [13]. However, the conclusions of our study, given its retrospective nature, have been heavily criticized [21]. Arguments against adjuvant mitotane are based on the methodological flaws of the available evidence, inherent complexity of mitotane treatment, and lack of factors predicting response to treatment and the toxicity profile of the drug [10].

More recently, 3 studies addressed the issue of adjuvant mitotane and provided evidence of its efficacy. Although the study from the M.D. Anderson Cancer Center claimed that a state-of-the-art surgical approach may provide a similar survival to surgery plus adjuvant mitotane, the lack of adjuvant mitotane treatment was a factor predicting a higher risk of recurrence [23]. Moreover, a small cohort of patients treated with adjuvant mitotane had a better disease-free survival notwithstanding that they were treated by less experienced surgeons outside the institution; however, adjuvant mitotane did not affect overall survival [22]. Fassnacht and colleagues [23] found that survival was improved in patients with stage II ACC who were managed by a specialized center early after surgery compared to patients who were referred at a later stage, usually after tumor recurrence. Adjuvant mitotane was more frequently used in the first group and treatment was associated with a survival advantage [23]. Wangberg and colleagues [24] reviewing their experience with ACC, showed that an aggressive surgical approach associated with the use of adjuvant mitotane was associated with a satisfactory disease-specific survival. The benefit of mitotane was evident for patients with high-stage ACC and circulating drug levels >14 mg/l [24].

Controversy on adjuvant mitotane is deemed to continue unless results of prospective, controlled studies become available. We have launched the first randomized trial in an adjuvant setting for ACC, the ADIUVO study, (http://www.adiuvo-trial.org) under the endorsement of the European Network for the Study of Adrenal Tumours (ENS@T). The study's aim is to assess the efficacy of adjuvant mitotane treatment in prolonging recurrence-free survival in patients with ACC at low-intermediate risk of recurrence. Results of ADIUVO may not be expected before 2017.

Management of adjuvant mitotane treatment

Nowadays, mitotane monitoring is readily available across Europe, where it is provided as a free service by the company distributing mitotane (info@lysodren-europe.com). Mitotane monitoring is a key for an appropriate management of adjuvant treatment giving the possibility to guide dose adjustments and target mitotane concentrations that have been associated with a therapeutic effect. Indeed, plasma mitotane levels >14 mg/l have been found to predict tumor response and improve survival in patients with advanced ACC [15, 16, 25]. Preliminary results of our group demonstrated that the concept of a relationship

between plasma concentrations of mitotane and its efficacy is applicable also to disease-free patients who are treated by means of adjuvant therapy [26].

At San Luigi Hospital, we recommend adjuvant mitotane in the patients perceived to be at high risk of recurrence, while the remainders are encouraged to enter the ADIUVO trial. Although our capability of predicting future risk of ACC recurrence after radical surgery and death is limited, it is generally agreed that stage III—IV ACC, margin-positive resection, and an elevated mitotic index are all factors portending an unfavorable prognosis [27]. Stage IV ACC may be susceptible to complete removal of the primary and metastatic tumor sites, but this condition may be assimilated to a margin-positive resection. Even if solid evidence is lacking, it is usually thought that these patients with stage IV tumors require postoperative medical treatment [28]. An elevated mitotic index is increasingly recognized as a negative prognostic factor and studies showed that cutoff values of 10 % for Ki-67 or 9 mitoses per high-power microscopic field were able to categorize patients at high risk of recurrence [28, 29].

In our practice, we start adjunctive mitotane treatment as soon as possible after surgery, in any case within 3 months. Although a high-dose regimen is able to provide therapeutic plasma concentrations of mitotane within 1 month in about one third of the patients [30], we are more cautious with dose escalation (Table 1). A high-dose regimen requires an intensive follow-up and may be more frequently associated with side effects, while our schedule is better tolerated and has less impact on the quality of life. Anyway, we are currently using higher doses than in the past [31] acknowledging the importance of shortening time necessary to reach target mitotane concentrations.

The most common unwanted effects are gastrointestinal manifestations that appear early, independently on mitotane levels. They can be managed with temporary dose reduction, or delay of dose increments, and supportive therapy. Elevated γ-glutamyltransferase levels are also frequently observed but are not actually troublesome unless values are exceedingly elevated. Clinically significant liver toxicity is characterized by a marked increase in transaminases and bilirubin, but is infrequently observed in the absence of predisposing conditions [3, 28, 30–32]. Central neurologic toxicity (cerebellar symptoms, disturbed cognitive performance) is more closely associated with elevated mitotane concentrations (>20 mg/l) but subtler symptoms, such as memory impairment or attention deficit, may be observed in some patients even when they are exposed to lower drug concentrations [15, 16, 32]. A great individual variability in the susceptibility to mitotane-related unwanted effects is apparent for causes that are still unknown.

Table 1 Practical guidelines to manage patients on adjuvant mitotane treatment

✔ Start with 1 g daily and increase mitotane dose every 4–7 days up to 8–10 g daily, or the maximum tolerated dose. Give mitotane in split doses with meals or snacks
✔ Accommodate mitotane schedule to patient's tolerance
✔ Aim at serum mitotane concentrations of 14–20 mg/l
✔ Check mitotane levels after 4 weeks from treatment start to adjust dosage
✔ Thereafter, check mitotane levels every 4–8 weeks until reaching target levels (14–20 mg/l). Then, mitotane dose can be reduced and levels checked less frequently
✔ In case of slight unwanted effects, continue mitotane and treat symptoms (e.g., nausea, diarrhea) accordingly
✔ In case of moderate side effects, step down to the previously tolerated dose and use symptomatic therapy
✔ In case of severe side effects, discontinue mitotane and institute specific treatment. Duration of treatment stop depends on clinics and mitotane levels. After interruption, restart with a lower dose
✔ At steady state, clinical assessment, biochemical, and hormonal evaluation, and monitoring of mitotane levels every 3–4 months, or in case of significant side-effects. Adjust mitotane dose according to circulating levels and tolerability

Recommendations based on personal experience

Because of the adrenolytic effect of mitotane, all patients should receive glucocorticoid replacement to prevent adrenal insufficiency. Steroid doses are typically higher than in Addison's disease, due to an enhanced metabolic clearance rate of glucocorticoids induced by mitotane [34]. An inadequate treatment of adrenal insufficiency increases mitotane-related toxicity, particularly gastrointestinal side-effects, and reduces tolerance [3, 28, 33]. Mineralocorticoid supplementation is not mandatory in all patients because the zona glomerulosa is partly spared by the toxic effect of mitotane [3, 28, 33]. Moreover, mitotane affects thyroid and gonadal function in a complex way by mechanisms that are still to be completely elucidated. Mitotane administration is associated with low FT4 levels without a compensatory rise in TSH, an effect that becomes apparent early in the course of treatment. This prompts thyroxin replacement, even if the benefit of this measure is difficult to appreciate [28, 32, 33]. In women, gonadal function is usually preserved and most female patients have regular cycles unless PRL levels are significantly increased [28, 32, 33] due to a weak estrogen-like action of mitotane [35]. Conversely, in men mitotane treatment causes sexual dysfunction as a late but common unwanted effect, due to inhibition of testosterone secretion. Sex steroid replacement may become necessary to treat erectile dysfunction in some patients but may worsen gynecomastia (Table 2) [28, 32, 33].

A general measure to deal with mitotane toxicity is a step down to the previously tolerated dose, or temporary

Table 2 Hormone replacement during adjuvant mitotane treatment

✔ Start glucocorticoid replacement at initiation of mitotane treatment
✔ Replace glucocorticoid at higher doses than usual (50 mg hydrocortisone–75 mg cortisone acetate, or even larger daily doses, may be needed in the long-term)
✔ Glucocorticoid replacement is monitored best with careful clinical assessment and measurement of electrolytes, since assessment of serum cortisol is confounded by the mitotane-induced increase in CBG. Assessment of UFC is confounded by enhanced steroid metabolism and current steroid supplementation
✔ Look for clinical and biochemical signs of mineralocorticoid deficiency in the long term; give fludrocortisone if needed
✔ Look for hypogonadism, particularly in long-term treated men, heralded by low free testosterone levels. Total testosterone may be normal due to the mitotane-induced increase in SHBG
✔ Replace testosterone in the event of erectile dysfunction or impotence. Gynecomastia may be simply due to the estrogenic effect of mitotane
✔ Low T4 levels associated with normal TSH are frequently observed. Replace thyroxin when T4 levels are markedly low and symptoms of hypothyroidism (somnolence, decreased attention) are apparent

Recommendations based on personal experience and Ref. [29]

CBG cortisol-binding globulin, *SHBG* sex-hormone binding globulin

drug withdrawal in the event of severe manifestations. However, well-informed and motivated patients are able to cope with side effects and maintain compliance to treatment. To accomplish this task, it is important to establish a close patient–physician relationship to induce and maintain adherence to treatment. Patients seek advice frequently, also because their local physicians are unfamiliar with mitotane use and its attendant complications, and it is necessary to give a timely counseling to keep patients on treatment.

The optimal duration of therapy remains undefined. Since most ACC recurrences after complete resection occur within 2 years from primary surgery, in our practice we consider such a period as a landmark [28, 33]. However, we are eager to prolong treatment if well tolerated in patients at elevated risk.

Conclusion

Whenever ACC is completely removed we should face the dilemma to treat by means of adjuvant therapy or not. In our opinion, adjuvant mitotane is the preferable approach in most cases, because the majority of patients referred to our institution following adrenalectomy have an elevated risk of recurrent disease.

A better understanding of factors that influence prognosis and response to treatment [36, 37] will help in stratifying patients according to their probability of benefiting from adjuvant mitotane, with the aim of sparing unnecessary toxicity to patients who are likely unresponsive. However, until significant advancements take place, we have to deal with uncertainty using our best clinical judgement and personal experience in the clinical decision process.

Conflict of interest There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

1. B.L. Wajchenberg, M.A. Albergaria Pereira, B.B. Medonca et al., Adrenocortical carcinoma: clinical and laboratory observations. Cancer **88**, 711–736 (2000)
2. A.P. Dackiw, J.E. Lee, R.F. Gagel, D.B. Evans, Adrenal cortical carcinoma. World J. Surg. **25**, 914–926 (2001)
3. B. Allolio, M. Fassnacht, Adrenocortical carcinoma: clinical update. J. Clin. Endocrinol. Metab. **60**, 273–287 (2006)
4. R. Bellantone, A. Ferrante, M. Boscherini et al., Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the italian national registry for adrenal cortical carcinoma. Surgery **122**, 1212–1218 (1997)
5. P. Icard, P. Goudet, C. Charpenay et al., Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the french association of endocrine surgeons study group. World J. Surg. **25**, 891–897 (2001)
6. R.F. Pommier, M.F. Brennan, An eleven-year experience with adrenocortical carcinoma. Surgery **112**, 963–970 (1992)
7. D.E. Schteingart, A. Motazedi, R.A. Noonan, N.W. Thompson, Treatment of adrenal carcinomas. Arch. Surg. **117**, 1142–1146 (1982)
8. B. Bodie, A.C. Novick, J.E. Pontes et al., The cleveland clinic experience with adrenal cortical carcinoma. J. Urol. **141**, 257–260 (1989)
9. A.A. Nelson, G. Woodard, Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). Arch. Pathol. **48**, 387–394 (1949)
10. I. Veytsman, L. Nieman, T. Fojo, Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. J. Clin. Oncol. **27**, 4619–4629 (2009)
11. S. Hahner, M. Fassnacht, Mitotane for adrenocortical carcinoma treatment. Curr. Opin. Investig. Drugs. **6**, 386–394 (2005)
12. L. Cerquetti, C. Sampaoli, D. Amendola et al., Mitotane sensitizes adrenocortical cancer cells to ionizing radiations by involvement of the cicli B1/CDK complex in G2 arrest and mismatch repair enzymes modulation. Int. J. Oncol. **37**, 493–501 (2010)
13. D.E. Schteingart, Adjuvant mitotane therapy of adrenal cancer–use and controversy. N. Engl. J. Med. **356**, 2415–2418 (2007)
14. R. Vassilopoulou-Sellin, V.F. Guinee, M.J. Klein et al., Impact of adjuvant mitotane on the clinical course of patients with adrenocortical cancer. Cancer **71**, 3119–3123 (1993)
15. H.R. Haak, J. Hermans, C.J. van de Velde et al., Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br. J. Cancer **69**, 947–951 (1994)
16. E. Baudin, G. Pellegriti, M. Bonnay et al., Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o, p'DDD) levels on

the treatment of patients with adrenocortical carcinoma. Cancer **92**, 1385–1392 (2001)
17. L. Barzon, F. Fallo, N. Sonino, O. Daniele, M. Boscaro, Adrenocortical carcinoma: experience in 45 patients. Oncology **54**, 490–496 (1997)
18. D.E. Schteingart, G.M. Doherty, P.G. Gauger et al., Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr. Relat. Cancer **12**, 667–680 (2005)
19. M. Terzolo, A. Angeli, M. Fassnacht et al., Adjuvant mitotane treatment for adrenocortical carcinoma. N. Engl. J. Med. **356**, 2372–2380 (2007)
20. J. Bertherat, J. Coste, X. Bertagna, Adjuvant mitotane in adrenocortical carcinoma. Letter to the Editor. N. Engl. J. Med. **357**, 1256–1257 (2007)
21. H. Huang, T. Fojo, Adjuvant mitotane for adrenocortical cancer–a recurring controversy. J. Clin. Endocrinol. Metab. **93**, 3730–3732 (2008)
22. E.G. Grubbs, G.G. Callender, Y. Yan Xing et al., Recurrence of adrenal cortical carcinoma following resection: surgery alone can achieve results equal to surgery plus mitotane. Ann. Surg. Oncol. **17**, 263–270 (2010)
23. M. Fassnacht, S. Johanssen, W. Fenske et al., Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers. J. Clin. Endocrinol. Metab. **95**, 4925–4932 (2010)
24. B. Wängberg, A. Khorram-Manesh, S. Jansson et al., The long-term survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane. Endocr. Relat. Cancer **17**, 265–272 (2010)
25. I.G. Hermsen, M. Fassnacht, M. Terzolo et al., Plasma concentrations of o, p'DDD, o, p'DDA, and o, p'DDE as predictors of tumor response to mitotane in adrenocortical carcinoma: results of a retrospective ENS@T multicenter study. J. Clin. Endocrinol. Metab. **96**, 1844–1851 (2011)
26. A. Ardito, A. Al Ghuzlan, M. Fassnacht et al., Mitotane levels affect the outcome of patients treated adjuvantly following radical resection of adrenocortical cancer (ACC), in *93th Endocrine Society Meeting*, Boston, 4–7 July 2011
27. A. Berruti, M. Fassnacht, E. Baudin et al., Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel. J. Clin. Oncol. **28**, e401–e402 (2010)
28. M. Fassnacht, R. Libé, M. Kroiss, B. Allolio, Adrenocortical carcinoma: a clinician's update. Nat. Rev. Endocrinol. **7**, 323–335 (2011)
29. M. Volante, E. Bollito, P. Sperone et al., Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. Histopathology **55**, 535–543 (2009)
30. S. Mauclère-Denost, S. Leboulleux, I. Borget et al., High-dose mitotane strategy in adrenocortical carcinoma: prospective analysis of plasma mitotane measurement during the first 3 months of follow-up. Eur. J. Endocrinol. **166**, 261–268 (2012)
31. M. Terzolo, A. Pia, A. Berruti et al., Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. J. Clin. Endocrinol. Metab. **85**, 2234–2238 (2000)
32. F. Daffara, S. De Francia, G. Reimondo, B. Zaggia, E. Aroasio, F. Porpiglia, M. Volante, A. Termine, F. Di Carlo, L. Dogliotti, A. Angeli, A. Berruti, M. Terzolo, Prospective evaluation of mitotane toxicity in adrenocortical cancer patients treated adjuvantly. Endocr. Relat. Cancer **15**, 1043–1053 (2008)
33. M. Terzolo, A. Berruti, Adjunctive treatment of adrenocortical carcinoma. Curr. Opin. Endocrinol. Metab. **15**, 221–226 (2008)
34. R.V. Hague, W. May, D.R. Cullen, Hepatic microsomal enzyme induction and adrenal crisis due to o, p'DDD therapy for metastatic adrenocortical carcinoma. Clin. Endocrinol. **31**, 51–57 (1989)
35. N. Nancy Nader, G. Raverot, A. Emptoz-Bonneton et al., Mitotane has an estrogenic effect on sex hormone-binding globulin and corticosteroid-binding globulin in humans. J. Clin. Endocrinol. Metab. **91**, 2165–2170 (2006)
36. Y.Z. Xu, Y. Zhu, Z.J. Shen, J.Y. Sheng, H.C. He, G. Ma, Y.C. Qi, J.P. Zhao, Y.X. Wu, W.B. Rui, Q. Wei, W.L. Zhou, X. Xie, G. Ning, Significance of heparanase-1 and vascular endothelial growth factor in adrenocortical carcinoma angiogenesis: potential for therapy. Endocrine **40**, 445–451 (2011)
37. J. Ye, Y. Qi, W. Wang, F. Sun, Q. Wei, T. Su, W. Zhou, Y. Jiang, W. Yuan, J. Cai, B. Cui, G. Ning, Lower expression of ATM and gene deletion is more frequent in adrenocortical carcinomas than adrenocortical adenomas. Endocrine **41**, 479–486 (2012)