Adjuvant Mitotane for Adrenocortical Cancer—Working through Uncertainty

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The Journal of Clinical Endocrinology & Metabolism recently published a commentary by Huang and Fojo (1) offering a skeptical view on the efficacy of mitotane as an adjunctive postsurgical measure in patients with adrenocortical cancer (ACC). Their commentary focused on outlining the limitations of our recent study which indicated that adjuvant mitotane may prolong recurrence-free survival (RFS) in patients with radically resected ACC (2). However, we do not agree with several of their conclusions and believe that it is of interest to present our view for a balanced and comprehensive coverage of this important matter.

In principle, we agree with Huang and Fojo that our study suffers from the important limitation of a retrospective analysis; thus our investigation should be considered as hypothesis generating and certainly does not provide conclusive evidence. This problem has been clearly acknowledged in the paper, and we cautiously concluded that our study should renew interest in adjuvant therapy, whereas prospective, randomized trials will be needed to confirm the efficacy of adjuvant mitotane treatment (2). However, the rarity of ACC precluded organization of a randomized trial either in an adjuvant setting or in patients with advanced ACC (3). Nonetheless, mitotane has been used for treating patients with ACC since the 1960s and is the only drug approved for ACC by the U.S. Food and Drug Administration and the European Medicines Evaluation Agency (4). In this scenario, a study including all consecutive patients treated postoperatively with mitotane in some centers and all consecutive patients left untreated after operation in other centers is the best way to obtain explorative data on the efficacy of adjuvant mitotane, provided that the two groups are comparable. In our study, in fact, mitotane was recommended on the basis of the treatment policy of the center, independent of the characteristics of either the tumors or the patients, and this is a major advantage minimizing selection bias as compared with other studies that had less clear treatment assignments (5).

The major criticism of Huang and Fojo (1) is that we did not demonstrate any benefit on overall survival (OS) for patients treated adjuvantly. However, this is not correct because the hazard ratio of death of the German cohort of nontreated patients was nonsignificantly higher than mitotane-treated patients in univariate analysis, but the difference became significant in multivariate analysis after adjusting for imbalances in prognostic factors (the German cohort included more patients with stage I and II ACC than the Italian cohort of mitotane-treated patients). Even when we accept that the effect of adjuvant mitotane on OS was less impressive than on RFS, we disagree that prolonging a disease-free status is not a clinically meaningful objective even without extending significantly duration of life. In addition, there is a long-standing debate on the most appropriate endpoint for adjuvant trials, and both OS and RFS have been suggested. Analysis of RFS has the advantage of needing a shorter follow-up and being directly related to the treatment tested. The most important disadvantage of RFS is its close relationship to the frequency and quality of evaluation. Bias in follow-up or ascertainment of outcome in observational retrospective series is well recognized, and we have acknowledged this potential limit of our study. However, the follow-up procedures were highly comparable among the different centers and included imaging evaluation of the chest and abdomen every 6 months until disease progression or the end of the study period (2). Even if survival has to be considered as the reference end-point, it may not be a direct result of the study drug because it may be strongly influenced by subsequent treatments and oncologists are increasingly considering RFS as a valid surrogate for OS (6). However, this relationship has never been demonstrated specifically in ACC patients.

Another criticism is derived from an ill-conceived reanalysis of our data. Huang and Fojo (1) aimed at demonstrating that the time interval between ACC recurrence and death is higher in patients treated adjuvantly than patients left untreated after surgery. Thus, they assumed important differences in tumor biology of the different cohorts. This conclusion comes from subtracting median time to recurrence from median survival observed in the

Abbreviations: ACC, Adrenocortical cancer; OS, overall survival; RFS, recurrence-free survival.
different groups of patients. However, this analysis is flawed by application of descriptive statistics to time series not taking into consideration censored observations and deaths not related to ACC. Therefore we have analyzed the survival after recurrence in our cohorts and found no difference.

Moreover, Huang and Fojo (1) argue that a median duration of treatment of 29 months can hardly explain a median time to recurrence of 42 months in the adjuvant group. However, we reported that treatment duration ranged between 6 and 164 months (2), and such a wide range clearly means that there were patients discontinuing mitotane early after a relapse and patients continuing mitotane for long periods. In our paper, it is indeed stated that 21 patients were treated for 4 yr or more, suggesting that mitotane had much to do with the long survival of such patients.

After having criticized our findings, Huang and Fojo (1) agree that adjuvant mitotane can prolong RFS in patients after complete resection presenting with unfavorable prognostic factors, and they propose the interesting theory that continuing mitotane indefinitely might prolong survival. We find this hypothesis attractive, and we accept that a longer duration of treatment may have a stronger impact on survival. Huang and Fojo suggest a low-dose regimen (<3 g/d), but we have recently demonstrated that the time to reach target levels was more than 6 months in some patients (7). Because recurrences occur in a significant proportion of patients within the first 6 months (2, 3), a low-dose regimen may not be fully coherent with a concept of adjuvant therapy (8). It is our current practice in most patients in good clinical conditions to administer 5–7 g mitotane per day until a mitotane concentration above 14 mg/liter is reached and then to adapt dosage according the blood level for a duration of 2–3 yr. We consider continuing treatment indefinitely in selected cases. In our experience, side effects are frequent, but well-informed and motivated patients are able to cope with them without discontinuing treatment permanently by applying a careful tailoring of the mitotane schedule guided by monitoring of drug levels (9).

In conclusion, there are many areas of uncertainty concerning adjuvant mitotane treatment, but in our opinion there is evidence that this approach may benefit a number of patients with ACC. The heart of the problem is to understand heterogeneity in tumor biology that is responsible for discrepancies in outcome among treated patients. Differences in the ability to metabolize and activate mitotane by tumor cells (5) or the secretory status of ACC (10) may be factors affecting response to treatment. The only way to answer the open questions is by performing randomized trials. Therefore, we have designed a trial for patients at low to intermediate risk of recurrence who are randomized for mitotane vs. observation only (ADIUVO trial) under the endorsement of the European Network for the Study of Adrenal Tumors. However, the majority of patients with ACC may be qualified as being at high risk for recurrence because the 5-yr recurrence rate of some 200 patients after radical resection is greater than 65% (unpublished data from the German ACC Registry, M. Fassnacht and B. Allolio). Therefore, further clinical trials are needed. However, until results from randomized trials are available, we have to deal with uncertainty, and clinical judgment and personal experience play an important role in care of patients with ACC.

Acknowledgments

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Disclosure Summary: M.T., M.F., G.C., B.A., and A.B. have nothing to declare.

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