Commentary: Adjuvant Mitotane for Adrenocortical Cancer—A Recurring Controversy

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Adrenocortical cancer (ACC) is a tumor with a high mortality, often complicated by hypercortisolism. Because of its rarity, physicians must rely on anecdotal evidence, uncontrolled trials, and retrospective studies. Mitotane is the only drug approved by the U.S. Food and Drug Administration for ACC. Interest in mitotane dates to the 1960s when studies demonstrated its ability to 1) inhibit adrenocortical steroid biosynthesis by inhibiting cholesterol side chain cleavage and 11 β-hydroxylation and 2) affect extraadrenal disposition of cortisol by inducing hepatic clearance (1, 2). Over the years, mitotane has been at the center of many controversies because of its limited efficacy and associated toxicities. In this opinion, we address the use of adjuvant mitotane in ACC, a recurring controversy again under debate (3, 4).

When using anticancer agents as adjuvant therapy, the goal is to impact outcome by starting therapy soon after surgery. Clinically, use as an adjuvant therapy usually follows demonstration of the agent's activity in metastatic disease, and for mitotane, this evolution began in the 1960s with several studies reporting biochemical and tumor regression rates as high as 85% (5–7). Unfortunately, these high response rates were not substantiated in subsequent trials, and it now appears measurable reduction in tumor sufficient to qualify for a partial response occurs in at most 5–30% of patients with ACC treated with mitotane. Rarely is a complete regression achieved. These discrepancies are explained in part by more accurate imaging tools and the possibility that in early studies, efficacy assessment may have been influenced by the drug's effect on hormone production. As often observed clinically, mitotane can improve symptoms of hormone excess despite increasing tumor burden, and this likely influenced early efficacy assessments.

Studies evaluating adjuvant mitotane are mostly carefully assessed anecdotes that inform the clinician with an interest in ACC (see supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). However, the data have limited value because clinical and biochemical variables that might be agreed as important vary or have not been evaluated. For example, different outcomes might be expected depending on the number of patients undergoing surgical resection as well as the stage of the tumor and its size and weight; fewer surgeries and larger tumors would be adverse factors. Similarly, hormone production might be expected to influence results; patients with Cushing's, for example, might do less well. As for the therapy, the proximity to surgery when mitotane is started, the dose, and the treatment duration would also be expected to impact the outcome–a delay in starting therapy, administration of suboptimal doses, and a brief treatment duration would be considered less optimal. Finally, the duration of follow-up and the endpoints chosen could alter results because mitotane might only delay time to recurrence without affecting overall survival such that shorter follow-ups might overstate benefit. Accepting these as important variables, it becomes clear as one inspects the disparate data why published results are conflicting.

Add to this eclectic collection of data the most recent entry, a retrospective analysis of 177 patients with ACC who underwent radical surgery at eight centers in Italy and 47 centers in Germany between 1985 and 2005 (3). The treatment group consisted of 47 Italian patients who received adjuvant mitotane after radical surgery (mitotane group). Their outcome was compared with that of 55 Italian and 75 German patients (control groups 1 and 2, respectively) who did not receive adjuvant mitotane after surgery. The authors concluded adjuvant mitotane prolongs recurrence-free survival in patients with radically resected ACC. Aside from the skepticism all retrospective analyses in a rare disease deserve, we believe possible flaws in the study preclude the limited conclusions reached.

Terzolo *et al.* do not claim an improvement in overall survival because the difference with control group 2 is not statistically significant (3). Furthermore, we believe that as the data mature, a lack of a mitotane effect on survival will become unequivocal because there were many patients in the mitotane group with follow-up of less than 5 yr as of the date of the report. And if mitotane only delays time to recurrence without affecting survival, this would be a disappointing outcome of limited value. We would also note an observation that in our view questions mi-

Abbreviation: ACC, Adrenocortical cancer.

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totane's efficacy, even as a drug that can prolong time to recurrence. Overlooked, but of great import, is what happened after patients suffered a recurrence. Time to recurrence, the first milestone assessed, occurred in control group 1, control group 2, and the mitotane group at 10, 25, and 42 months, respectively. A first recurrence is in our opinion important, because it resets the clock. There is nothing said, nor do we have reason to believe, that the pattern or severity of recurrences was different among groups. There is also no evidence to suggest their management differed. Indeed, according to the authors, "among patients in all groups, recurrences were managed with surgery (56.2%), mitotane (70.3%), cytotoxic chemotherapy (42.2%), or other therapies (7.5%); these approaches were often used in combination." Given the similarities in management, one wonders why both control groups then have an interval of 42 months (52−10 and 67−25) to the next milestone (overall survival), whereas the mitotane group has a 60% greater interval of 68 months (110−42) before reaching the overall survival milestone at 110 months. The authors report the median duration of mitotane treatment was 29 months. This means mitotane had been stopped more than a year before documentation of recurrences in the mitotane cohort at 42 months, excluding much if any role for a residual mitotane effect despite the drug's long half-life. Unable to explain a straightforward effect of mitotane on the clinical course after a first recurrence, we are left searching for explanations that might explain the tentative results.

It is possible adjuvant mitotane in some way changed the biology of the ACCs such that recurrences were less aggressive. Although we cannot exclude this possibility, it would be a first in oncology that a drug with very limited efficacy in advanced disease profoundly alters the intrinsic tumor biology making it less aggressive at the time of recurrence – an explanation we do not believe. Alternately the better overall survival of the mitotane group may be explained by an undetected selection bias that randomized patients with a better prognosis and more biologically favorable tumors to the mitotane group. We would note that Terzolo *et al.* say, "adjuvant mitotane was routinely recommended at four of the Italian centers," but do not say all patients received such therapy (47 patients enrolled at four centers over 20 yr is an average of about one patient every other year). Such a bias could also invalidate the conclusion that adjuvant mitotane prolonged recurrence-free survival. However, it is also possible that adjuvant mitotane delayed disease recurrence, and because it was prematurely discontinued had no effect on overall survival.

Although one might question the conclusions, like many clinicians who treat patients with ACC, we agree with the authors that adjuvant mitotane can help prolong the disease-free interval in some patients. We believe adjuvant mitotane should be considered in patients who have undergone complete resections, especially those with histologically unfavorable tumors and/or small surgical margins. In this regard, we would stress a point made by Terzolo *et al.* (4, 8) in response to correspondence should not be overlooked. They noted that "serum mitotane concentrations were monitored in a subgroup of 22 patients; in all these patients mitotane concentrations higher than 14 mg per liter were reached." This is important because two small studies that have not been validated suggest antitumor activity requires serum mitotane values greater than 10–14 mg/liter (9, 10). Furthermore, the authors noted that "16 of the 22 patients in whom serum mitotane concentrations were monitored received a daily mitotane dose that was 3 g or less." This too is important because lower doses are much better tolerated, and we feel that in the adjuvant setting, physicians should consider lower doses that eventually achieve therapeutic levels, even if after a longer time interval. We believe it is more important to sustain therapy for as long as possible because it is likely mitotane is not cytotoxic and does not kill residual malignant cells but only delays growth and in turn recurrences. If the latter is true, then continuing mitotane indefinitely might prolong survival. We also feel strongly this should be done with the least impact on the quality of their lives, and this is more likely to be achieved with lower doses that eventually can reach the levels of 14–20 mg/liter recommended by many. Furthermore, we would highlight the observation by Terzolo *et al.* that "adverse events associated with mitotane were mainly of grade 1 or 2" (3). We would argue the Common Terminology Criteria for Adverse Events scale was developed for agents administered intermittently that have transient toxicities and is not applicable to an oral agent taken daily for years. A grade 1 or 2 toxicity is tolerable for a few days, but not for months or a lifetime. So this is an invalid way to assess toxicity and should not be used in any prospective randomized study.

In summary then, we feel the recently reported study suffers from problems common to many retrospective studies and don't support a recommendation of adjuvant mitotane for all patients. However, we agree it should be considered in selected patients with completely resected ACC and poor prognostic features including but not limited to those that comprise the Weiss score. In these patients, we favor administering mitotane at lower doses. Finally, we would propose that in most patients, mitotane does not kill cancer cells, but only delays their growth, explaining a beneficial effect on time to recurrence but not overall survival. If growth delay is its predominant activity, then indefinite therapy may help not only to delay a recurrence but also to increase overall survival. And although indefinite mitotane might not be attractive, in a patient tolerating therapy well, the alternative, recurrence and death, argue for indefinite therapy. Because a study addressing indefinite mitotane may never be conducted, in this rare disease, such decisions will require a clinician's judgment.

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