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Comparison of Two Mitotane Starting Dose Regimens in Patients With Advanced Adrenocortical Carcinoma

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Context: Mitotane is the only approved drug for treatment of adrenocortical carcinoma. Its pharmacokinetic properties are not fully elucidated and different dosing regimens have never been compared head to head.

Objective: The objective of the study was to investigate the relationship between mitotane dose and plasma concentration comparing two dosing regimens.

Design/Setting: This was a prospective, open-label, multicenter trial of a predefined duration of 12 weeks.

Patients/Interventions: Forty mitotane-naïve patients with metastatic adrenocortical carcinoma were assigned to a predefined low- or high-dose regimen by the local investigator. Thirty-two patients could be evaluated in detail.

Main Outcome Measure: The difference in median mitotane plasma levels between both treatment groups was measured.

Results: Despite a difference in mean cumulative dose (440 _ 142 g vs 272 _ 121 g), median maximum plasma levels were not significantly different between the two groups [high dose 14.3 mg/L (range 6.3–29.7, n _ 20) vs 11.3 mg/L (range 5.5–20.0, n _ 12), P _ .235]. Ten of 20 patients onthe high-dose regimen reached plasma concentrations of 14 mg/L or greater after 46 days (range 18–81 d) compared with 4 of 12 patients on the low-dose regimen after 55 days (range 46–74 d, P _ .286). All patients who reached 14 mg/L at 12 weeks displayed a level of 4.1 mg/L or greater on day 33 (100% sensitivity). There were no significant differences in frequency and severity of adverse events. Among patients not receiving concomitant chemotherapy mitotane exposure was higher in the high-dose group: 1013 _ 494 mg/L _ d vs 555 _ 168 mg/L _ d (P _ .080).

Conclusions: The high-dose starting regimen resulted in neither significantly different mitotane levels nor a different rate of adverse events, but concomitant chemotherapy influenced these results. Thus, for mitotane monotherapy the high-dose approach is favorable, whereas for combination therapy a lower dose seems reasonable.

Current medical treatment of advanced adrenocortical carcinoma (ACC) is based on mitotane given either as monotherapy or combined with cytotoxic chemotherapy (1, 2). Mitotane is registered in the United States since 1970 for the treatment of advanced ACC and was in 2004 also authorized by the European Medicines Agency. Despite this long history of use, its mechanism of action and pharmacokinetic properties are not fully elucidated (3).

There is evidence of a correlation between mitotane plasma levels and antineoplastic efficacy. Studies have demonstrated an objective response rate of 55%–66% in patients whose plasma levels were above 14 mg/L, whereas lower levels were associated with lack of efficacy (4–6). The concept that mitotane levels predict treatment response has been confirmed in a large multicenter study (7). Accordingly, monitoring plasma levels is considered to be as standard of care.

Information on mitotane pharmacokinetics primarily originates from a study performed in 1960 (8). It appears that 35%–40% of the drug is absorbed from the gastrointestinal tract and is stored primarily in adipose tissues.

This may explain the time lag of 4 weeks to several months necessary for reaching target plasma levels (9 –12). Thus, higher starting doses have been proposed to earlier reach the therapeutic window (13). In addition, some groups suggested that mitotane plasma level after 2–4 weeks might predict whether the patient reaches the target level within a short time, justifying monotherapy in these patients (2, 13).

Metabolism of mitotane results in the formation of two metabolites, 2,4-dichlorodiphenyl acetic acid (DDA) and

1,1-(o,p_-dichlorodiphenyl)-2,2-dichloroethene (DDE), of whichDDAhas been identified as the major circulating and excreted metabolite (14). A recent retrospective study in a group of 91 patients with ACC demonstrated that DDA plasma levels greater than 92 mg/L may be associated with tumor response (7).

Tolerability is a matter of concern because adverse effects occur frequently and are also related in part to drug levels. However, the number of patients who discontinue therapy can be minimized by regular counseling about the management of adverse effects, careful adjustment of hormone replacement therapies, and tailoring of mitotane dosage based on plasma levels and side effects (15).

The recently completed first randomized trial in advanced ACC [First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT)] compared two chemotherapy regimens and established etoposide, doxorubicin, and cisplatin (EDP) plus mitotane as first-line cytotoxic chemotherapy for patients with ACC (16). The present study was nested within FIRM-ACT with the aim to better understand the relationship between mitotane dose (daily and cumulative) and plasma concentrations by comparing two predefined starting regimens (high dose and low dose). Secondary objectives were to evaluate the safety of mitotane and its impact on various hormonal parameters. Time to reach a mitotane plasma level of 14 mg/L was determined as a post hoc end point. In addition, we examined whether mitotane levels assessed early in therapy were predictive for reaching 14 mg/L within 12 weeks.

This is the first prospective multicenter study aimed at

improving knowledge on the pharmacokinetic properties of mitotane.

Materials and Methods

Patients

The main eligibility criteria were histologically confirmed locally advanced or metastatic adrenocortical carcinoma not amenable to radical surgical resection, radiologically monitorable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, life expectancy longer than 3 months, age 18 years or older, adequate hematological and biochemical function, effective contraception, written informed consent, and the ability to comply with study procedures. Exclusion criteria were previous treatment with mitotane, cytotoxic chemotherapy or experimental drugs for ACC, history of prior malignancy, renal or hepatic insufficiency, pregnancy, breast-feeding, presence of active infection, decompensated heart failure, myocardial infarction, or revascularization procedure in the last 6 months. The protocol was approved by the institutional ethics committees and all patients gave informed consent.

Study design and treatment

The study was an international prospective, open-label, multicenter study. Treatment with mitotane was initiated at least 2 weeks prior to the start of cytotoxic chemotherapy. Assignment to one of two dosing regimens was at the discretion of the local investigator without detailed inclusion criteria. A detailed summary of both regimens is provided in Table 1. Mitotane was taken orally in three daily doses with food. The predefined study duration for each patient was 12 weeks.

Measurement of mitotane and metabolites

Mitotane plasma level was assessed weekly during the first 8 weeks and then at weeks 10 and 12. Sampling was performed in

the morning at least 12 hours after the last dose. Quantitative analyses of mitotane,DDA,andDDEwere performed by Parexel (Bloemfontein, South Africa) using HPLC (17).

Safety assessments

Adverse events (AEs) were monitored throughout the study and assessed with the use of the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events version 2.0. Dosing of iv chemotherapy in case of hematological, renal, and neurological toxicity was done according to the study protocol. Mitotane dose was adjusted in case of grade 3/4 gastrointestinal AE and/or grade 2–4 central nervous system (CNS) AE (Table 1). In case of greater than grade 3 nonhematological toxicity (except alopecia) both mitotane and chemotherapy were temporarily discontinued. Liver enzymes [serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, _-glutamyltransferase (GGT)] were analyzed at baseline, week 4, and week 12.

Endocrine work-up

All hormone analyses were performed using validated assay methods by Bicêtre Hospital (Department of Endocrinology, Paris, France). TSH, free FT_3 (FT3), free T_4 (FT4), T_4-binding globulin (TBG), and SHBG (or sex hormone binding protein) were measured at baseline and at weeks 4 and 12. Total and free T, FSH, andLHwere measured before treatment and at week 12.

Statistical analysis

Only limited data were available on inter- and intrasubject variability of mitotane pharmacokinetics, precluding a classical sample size calculation. It was estimated that it would be necessary to recruit eight patients per subgroup (high/low dose, EDP/streptozotocin chemotherapy) to investigate differences between both dosing regimens and to evaluate safety. Assuming some dropouts, the study aimed at an inclusion of 40 patients.

The following pharmacokinetic parameters were calculated per protocol: plasma concentration before morning dose; highest plasma concentration observed (C_{max}); time to reach C_{max}; and area under the concentration-time curve (AUC_{0-t}). The post hoc end point median time to reach a mitotane plasma level of 14 mg/L was measured in days among patients in both regimens. The predictive value of early mitotane levels was examined using receiver-operating characteristic analyses. Data on thyroid and sex hormones are displayed according to mitotane plasma level. Adverse events are displayed according to severity and dosing regimen. Results are expressed as mean _ SD or median and range as indicated. Data were analyzed by the Biostatistics Unit of BIOTRIAL.

Results

Patient characteristics

Forty patients were enrolled in the study between 2004 and 2009. There were 19 men (48%) and 21 women (52%), mean age was 51 years, and mean body mass index was 25.3 kg/m_2. Table 2 displays demographic data according to the subgroups. Because all participants had to sign informed consent for the FIRM-ACT study at inclusion, the intention was to administer chemotherapy to all participants. However, 17 patients were not randomized in FIRM-ACT and did not receive chemotherapy during this substudy due to indolent disease (n _ 8), rapid progression of disease (n _ 3), patient's refusal (n _ 2), early death (n _ 2), revision of tumor staging (n _ 1), or violation of inclusion criteria (n _ 1).

As stated in the study protocol, all 40 patients were included in safety analyses. Eight patients were excluded from the per-protocol analysis of pharmacokinetics: three

patients died after 19, 21, and 24 days due to disease progression (n _ 2) and pulmonary embolism (PE) (n _ 1), respectively; in two patients protocol deviations resulted in missing at least three consecutive pharmacokinetic measurements, two patients did not respect the inclusion criteria and were rapidly excluded (after 4 and 6 d of treatment, respectively), and one patient refused to continue mitotane after 14 days (Figure 1).

From the remaining 32 patients, four patients were excluded from analyses concerning cumulative doses because they discontinued the study before the projected end point at week 12: one patient died after 39 days, one patient had severe CNS disorders (d 68), and two patients failed to comply with the protocol (d 65 and 71).

Mitotane cumulative dosage and plasma concentrations

Mean cumulative doses over the treatment period were substantially higher in the high-dose group (440 _ 142 g) compared with the low-dose group (272 _ 121 g). Ten of 20 patients on the high-dose regimen (50%) reached plasma concentrations of 14 mg/L or greater compared with 4 of 12 patients on the low-dose regimen (33%). In the high-dose group, this level was reached after a median of 46 days (range 18–81 d) compared with 55 days (range 46–74 d, P _ .286) in the low-dose group. Receiver-operating characteristic curves identified a plasma level of 6.0 mg/L on day 33 as the best compromise between sensitivity (86%) and specificity (61%) to predict attainment of the therapeutic level within 12 weeks. All patients who reached 14 mg/L displayed a level of 4.1 mg/L or greater on day 33 (100% sensitivity).

Mean cumulative dose needed to reach 14 mg/L was 291 _ 126 g (high dose) vs 137 _ 39 g (low dose, P _ .020). Median C_{max} was 14.3 mg/L (range 6.3–29.7 mg/L) in the high-dose group (n _ 20) and 11.3 mg/L (range 5.5–20.0 mg/L) in the low-dose group (n_12, P_.235). It should be noted that mitotane plasma levels in most patients were still rising and no plateau was reached within 12 weeks (Figure 2A). At the last visit in week 12, the median plasma level was 14.2 mg/L (range 2.1–29.7 mg/L) in the high-dose group and 10.6 mg/L (range 2.3–18.1 mg/L) in the low-dose group (P _ .120). Mitotane exposure was higher in the high-dose group but did not reach statistical significance ($AUC_{0–12\ weeks}$ 790 _ 444 mg/L _ d vs 543 _ 215 mg/L _ d, P _ .171).

Metabolites of mitotane

Median DDA C_{max} was 99.7 _g/mL (range 23.2–185.0_g/mL) in the high-dose group (n _ 20) and 88.0 _g/mL (range 35.4–102.0 _g/mL) in the low-dose group (n _ 12, Figure 2B).

Twelve of 20 high-dose patients (60%) reached DDA levels above 92 mg/L on at least one occasion compared with 3 of 12 in the low-dose regimen (25%) (P _ .076). Median time to reach aDDAlevel of 92 mg/L was 11 days after the start of treatment (high dose, n _ 12) vs 46 days (low dose, n _ 3). Of 15 patients reaching DDA plasma levels greater

than 92 mg/L, nine (60%) also had mitotane plasma levels above 14 mg/L, eight ofwhomwere treated according to the high-dose schedule.

Plasma concentrations of DDE were below the limit of quantification on most occasions. Nine patients on the high-dose regimen and two on the low-dose regimen presented measurable DDE values. In week 12, mean DDE plasma concentration among the high-dose patients was 0.67 _ 0.17 mg/L and 0.68 _ 0.15 mg/L in the low-dose group.

Effect of concomitant cytotoxic chemotherapy on mitotane plasma level

The mean cumulative mitotane dose in patients receiving chemotherapy in addition to mitotane (n _ 19) was comparable with the dose administered to 13 patientswho did not receive cytotoxic chemotherapy (358 _ 143 g vs 389_132 g; P_.574). Within the chemotherapy group, patients on the high-dose regimen had a median plasma level in week 12 of 9.2 mg/L (range 2.1–27.1 mg/L, n _ 12), and four patients reached plasma levels of 14 mg/L or higher. The median plasma level was not significantly different from patients on the low-dose regimen [10.8 mg/L (range 2.3–18.1 mg/L), n _ 7], of whom two patients reached the threshold of 14 mg/L.

Among patients not receiving chemotherapy, higher median plasma levels were observed in the high-dose

group: 18.3 mg/L (range 0.3–29.7 mg/L, n_8) compared with 10.3 mg/L (range 7.4–15.7 mg/L, n _ 5) in the lowdose group, but results were not statistically significant.

Figure 2. Median mitotane (A) and DDA (B) plasma concentration throughout the study in both dosing regimens.

The observation was reflected by a larger$AUC_{0–12}$ in this subgroup: 1013_494 mg/L _dvs555_168 mg/L _ d (P_.081).

Six of eight patients from the high-dose group reached a plasma level of 14 mg/L; in the low-dose group, this was reached by two of five patients.

Safety and toxicity

All 40 patients were evaluated for safety. A total of 200 AEs was reported, most of them were NCI-CTC grade 1 or 2 (n _ 166, Table 3). The remaining AEs were grade 3 (n_28) or grade 4 (n_6). The rate of AE per patient was similar in both groups (5.0 vs 5.2 AE/patient).

Almost half of all AEs (n_96, 48%) were related to the gastrointestinal system, mostly nausea (n _ 30), diarrhea (n _ 23), and vomiting (n _ 15). One grade 4 event was reported: gastrointestinal bleeding. The rate of gastrointestinal AEs per patient was slightly higher in the low-dose group (2.8 AE/patient vs 2.1 AE/patient).

There were eighteen AEs (9%) related to general disorders. General discomfort NCI-CTC grade 1 (n _ 6), asthenia (n _ 4), and fatigue (n _ 4) were most common events in this category. Most events were reported among patients on the high-dose regimen (n _ 16).

Fourteen AEs were related to metabolism and nutrition (7%); 10 occurred in the high-dose group. There were two grade 4 AEs: these were episodes of hypomagnesaemia and hypokalemia, both probably related to concomitant

cytotoxic treatment with EDP. There were four events in the low-dose group, all hypercholesterolemia grade 2 or less.

Eighteen events were related to disorders of the nervous system (9%). Vertigo (n _ 6) and dizziness (n _ 5) were mostcommon.Regarding psychiatric AEs, there were four reports of anxiety attacks and two reports of insomnia. Depression and hallucination were both reported once.

Changes in hepatic enzymes were seen frequently. After 12 weeks, the mean level of GGT was 361 _ 248 IU/L compared with 123 _ 191 IU/L at baseline. All patients had elevated GGT levels, with 89 IU/L being the lowest level. The mean level of serum glutamic oxaloacetic transaminase in week 12 was 46_24 IU/L, and the mean serum glutamic pyruvic transaminase was 52 _ 36 IU/L.

Four patients died during the study. Two patients died due to disease progression, one patient died after PE, and one patient died after severe cardiac failure, but these events were not considered drug related.

Hormonal parameters

Mean TSH did not change significantly over the course of this 12-week study, both in patients with high and low mitotane plasma levels (Table 4). In patients who did not reach a mitotane level of 14 mg/L (n_14), mean FT4 level in week 12 was 5.7 _ 4.5 pmol/L lower compared with baseline. The decrease was greater in patients with mitotane plasma levels greater than 14 mg/L: 7.7_3.2 pmol/L (n _ 11). Three patients already were on thyroid replacement therapy prior to the study. In three other patients, this was started during the study: two in the high-dose regimen and one in the low-dose regimen.

Mean TBG levels increased during the trial. Among patients who were evaluated in week 12, a mean increase of 5.1 _ 8.8 IU/mL was observed in those with mitotane levels below 14 mg/L (n _ 14). A mean increase of 7.2 _ 7.5 IU/mL was seen in patients with mitotane levels greater than 14 mg/L (n _ 11).

Analysis of sex hormones in males evaluated at week 12 showed a mean increase in LH level in week 12 of 4.5 _ 3.8 IU/L for those with mitotane levels below 14 mg/L (n_ 5). In patients with mitotane levels greater than 14 mg/L, the mean increase was 5.7 _ 3.8 IU/L (n _ 6).

The mean level of free T in males tended to decrease during the study, whereas the mean level of totalTin week 12 was not different from baseline. Mean SHBG levels were significantly higher in week 12 compared with baseline.

In females, the mean concentrations of FSH and LH in week 12 compared with baseline show variable results (not shown). Total and free T remained stable in female patients, whereas the mean concentration of SHBG was significantly increased.

Discussion

This is the largest prospective study on the pharmacokinetic properties of mitotane published so far. Despite the expected difference in cumulative dose at12weeks, neither the plasma concentrations of mitotane nor the time to reach a therapeutic level differed significantly between the two starting dose regimens. Area under the mitotane plasma concentration/ time curvewaslarger in the high-dose starting group, but this was not statistically significant. Also, the proportion of patients achieving the target plasma concentration within 12

weeks was higher in the high-dose group (10 of 20 vs 4 of 12, respectively). The beneficial effect of the high-dose schedule on mitotane exposure was stronger in a subgroup of patients not receiving chemotherapy.

Reaching the target concentration of 14 mg/L or greater is a major goal during mitotane treatment and has been associated with better response both in advanced diseaseandin adjuvantsetting (4–6, 18).Consequently,itseemsimportant to reach such concentrations as early as possible to rapidly establish antiproliferative efficacy, although this reasoning is not underpinned by clinical data.

In a previous study with 13 patients taking mitotane as first-line therapy, a correlation was observed between plasma levels and cumulative dose of mitotane (4). This suggests dose proportionality, which means that drug elimination is independent of the concentration present in the body (zero order reaction) rather than dependent (first order reaction). Therefore,wespeculate that in clinical practice elimination of mitotane proceeds at a constant rate independent of the plasma concentration. This is supported by the stable levels ofDDAthat were observed after 4 weeks of treatment in both groups. Consequently, administration of higher doses should result in higher plasma levels in a shorter period of time. Because steady-state levels of mitotane had not been reached at week 12, it is tempting to speculate that a longer study duration would have demonstrated that high-dose mitotane reaches steady-state conditions earlier.

Our data confirm previous observations that the increase in plasma concentrations is in general slow and highly variable. Obviously this behavior cannot be sufficiently explained by differences in dosing only, indicating that other

factors contribute to this observation. Potential explanations are related to effects on enzyme induction by concomitant drugs and differences in intestinal absorption, which may also be affected by ingested food. Also, recent data show that individual genetic differences are significantly associated with mitotane levels (19) like this is known for other drugs (20, 21). In the absence of baseline predictors, early measurements constitute the only signal whether a given patient hasahigh probability of reaching the therapeutic level in time (13).

The observation that the high-dose schedule results in higher exposure in patients not receiving concomitant chemotherapy may be explained by multiple factors. It is possible that patients do not tolerate high mitotane doses in addition to chemotherapy or that physicians anticipate on the addition of chemotherapy by lowering the mitotane dosage. However, cumulative doses were not different among these subgroups. Of note, treatment compliance could be a limitation in this respect. Also, the administration of cytotoxic chemotherapy could result in lower plasma levels due to drug interactions or impaired intestinal uptake (22).

No significant difference was detected between the two groups regarding the frequency and severity of adverse events. This suggests that actual dosage is not the key determinant of adverse effects. Of note, we did not observe any (significant) correlation between adverse events and mitotane plasma level. However, it has to be acknowledged that 18 patients (45%) never reached a plasma level above 14 mg/L, and only six patients had measurements above 20 mg/L. Nevertheless, in our personal experience,AEscan usually be managed by adequate support, even when given in

parallel to cytotoxic chemotherapy. An increase of GGT is well known and appeared in 100% of our patients. Observations in patients treated adjuvantly demonstrated that this is reversible (15, 23).

Mitotane can induce hormonal effects soon after the onset of treatment. After 12 weeks a significant decrease in FT4 was detectable with a trend for a negative correlation between mitotane and FT4 levels. TSH and FT3 remained unchanged or were increased. It is known from previous research that mitotane use can lead to biochemical findings mimicking central hypothyroidism, ie, low FT4 with approximately normal FT3 and TSH levels (15). Previously proposed explanations are a direct effect on the pituitary level, the induction of thyroid hormone metabolism, an increase in TBG levels, or changes in the thyroid hormone receptor's affinity for FT4 (22, 24, 25). Also, interference with FT3, FT4, and/or TSH assays cannot be excluded.

Data on the influence of mitotane on sex hormones are scarce. In vitro studies showed that mitotane increases the synthesis of steroid binding protein (26, 27). In our study, SHBG was markedly increased, whereas in males free T was decreased and LH was increased. Mitotane has been shown to bind the human estrogen receptor-_ with weak affinity, approximately 1000-fold weaker than that of estradiol itself (28). Although the concentration of mitotane in plasma is about 5.0_10^5 times higher than estradiol levels in men, the presence of increased levels of LH makes a strong estrogenic effect of mitotane at the pituitary level not likely. A recent study demonstrated significantly decreased levels of dihydrotestosterone in mitotane-treated patients, which might be the reason for the increase of gonadotrophins (29). Another

possibility is mitotane-induced inhibition of T secretion, set off at least partially by an increase inSHBGand by decreased production (30).

We acknowledge the limitations of our study. First, patients were not randomized to a dosing regimen, which could have introduced bias. However, due to theembedmentof the study within the FIRM-ACT protocol, a second randomization was judged to be not feasible. Second, protocol deviations produced missing data, which made the study underpowered in several analyses. Furthermore, we acknowledge that more patients in the high-dose group had to be excluded from the pharmacokinetic analyses. However, as mentioned in Results, the reasons for exclusion are unlikely treatment related, and therefore, we do not expect that this fact influenced the conclusions.Afourth limitation is that steady-state levels of mitotane were not reached in all patients. However, due to the aggressiveness of the disease, a longer, comprehensive pharmacokinetic study would be very challenging for patients and investigators. Finally, the study was underpowered to assess differences in subgroups.

In conclusion, the high-dose starting regimen led to higher mitotane plasma levels within 12 weeks of treatment, and more patients reached the target level of 14 mg/L. Observed differences were greater in the subgroup of patients who did not receive concomitant cytotoxic chemotherapy, but the results were not statistically significant due to lack of power. The rate of AEs was similar between both groups, leading us to conclude that the high-dose approach is the preferred strategy in patients with mitotane monotherapy. However, in patients with reduced tolerability (eg, due to concomitant cytotoxic chemotherapy), a less aggressive regimen might be

reasonable.

Acknowledgments

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