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Clinical results of the use of mitotane for adrenocortical carcinoma

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Abstract

Mitotane (o,p'-DDD) acts mainly as an inhibitor of intramitochondrial pregnenolone and cortisol synthesis. Its adrenolytic effect depends on metabolic activation due to conversion to o,p'-DDA and o,p'-DDE. The drug has been used for 40 years in the treatment of adrenocortical carcinoma, mainly its regional and metastatic stage, as an adjuvant to surgical resection of the tumor. In the medical literature there are controversial opinions about its efficacy for the treatment of adrenocortical carcinoma. In our experience, mitotane administered immediately after surgery appeared to be much more efficient than when administered later. We have administered this drug in all cases of microscopically confirmed adrenocortical carcinoma, irrespectively of stage at the time of surgery, for fear of a false too optimistic classification. In our series of 82 patients with adrenocortical carcinoma, 59 patients have been treated with mitotane, 32 of them immediately after surgery, and 27 with a delay of 2 to 24 months. Today there are 18 survivors in the group of patients treated with mitotane soon after the operation and only 6 survivors in the group receiving mitotane with a delay. All patients were simultaneously given replacement therapy. Undesired effects of mitotane administration included increased aminotransferase and alkaline phosphatase activity, decreased white cell, platelet or red cell number, and myasthenia. Furthermore, we used mitotane with good results in Cushing's syndrome of non-malignant origin as pre-treatment before surgery or in long-term treatment for patients with poor tolerance of other adrenal inhibitors.

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- Mitotane
- Adrenocortical carcinoma
- Cushing's syndrome

Introduction

Forty years ago Bergenstal et al. (1) published their first report on the beneficial effects of o,p'-DDD (1,1-(dichlorodiphenyl)-2,2-dichloroethane; mitotane) in adrenocortical carcinoma.

Mitotane inhibits the intramitochondrial conversion of cholesterol to pregnenolone and the conversion of 11-deoxycortisol to cortisol (2,3). It is also capable of producing selective adrenocortical necrosis, both in the adrenal tumor and in metastases. Additionally, it reverses gene-expressed chemotherapy resistance by reducing cellular drug efflux (4). The adrenolytic effect of mitotane depends on metabolic activation, o,p'-DDA and o,p'-DDE being the end products of the presumed metabolic activating pathway (5,6).

The annual incidence of adrenocortical carcinoma has been estimated at 0.5-2 per million (7). The introduction of new imaging

procedures may modify the data on the frequency of these tumors, because a significant number of clinically silent carcinomas are found in ultrasound scans. It is possible that the poor prognosis characteristic of adrenocortical carcinoma may change into a better one due to earlier detectability.

It is obvious that prognosis depends mainly on the rate of tumor expansion. The staging, according to the Surveillance, Epidemiology and End Result Classification (8), distinguishes localized, regional and metastatic (distant) forms of adrenocortical carcinoma. The staging system proposed by MacFarlane (9) distinguishes four stages: stage I (tumor less than 5 cm in diameter) and stage II (tumor more than 5 cm, not spreading into neighboring tissues), corresponding to a localized stage, stage III - corresponding to regional disease, and stage IV - corresponding to metastatic disease.

Surgery, sometimes aggressive (in stages III and IV), remains the basis of therapy. For many years mitotane has been considered to be the drug of choice for patients with inoperable, recurrent or metastatic adrenal carcinoma and has been administered mainly to treat these conditions. In recent years it has been advocated as a therapy following the resection of a localized tumor. In 1992 Wooten and King (10) cited 51 reports concerning tumor responses to mitotane, with the number of patients ranging from 1 to 75, and a total number of 551. Partial or total responses were noted in 194 of them (35.2%), and the best results (61%) were observed in the Lubitz series (11). Luton et al. (12) in 1990 used mitotane as adjuvant therapy after surgery in 59 patients; however, only eight had partial tumor regression. In our own 1995 report (13), mitotane administration resulted in remission in 12 out of 32 patients (37.5%).

The present study aimed at evaluating the results of mitotane therapy in the Department of Endocrinology (Center for Postgraduate Medical Education, Warsaw, Poland) during the last 33 years.

Material and Methods

Two groups of patients have been treated with mitotane in our department: group I consisting of patients with adrenocortical carcinoma, and group II consisting of patients with Cushing's syndrome of non-malignant origin.

Group I. Since 1966, 82 patients with adrenocortical carcinoma were referred to our department. There were 63 women and 19 men aged 13-70 years (mean 43.4). In 29 of them the adrenal tumor was found incidentally by ultrasound scan. In most patients in both groups, the tumor was diagnosed in the metastatic stage of the disease (Table 1). The size of the tumor ranged from 3.2 to 23.0 cm in the group of incidentally found masses and between 3.5 and 17.0 in the non-incidental group. Clinically silent adrenal tumors were diagnosed in 30 patients. Cushing's syndrome and virilization, often associated with hypertension, occurred most frequently in patients with hormonally active adrenal tumors (13). Four patients died just before surgery and two others immediately after the operation. Seventy-six other patients have been treated with surgery and/or with mitotane or cytostatic agents (Table 2).

Seventy-four patients were treated with surgery; four of them were submitted to partial hepatectomy and two to nephrectomy. Two patients with inoperable tumors only received mitotane in daily doses of 4.0-15.0 g. Sixty-one surgically treated patients received mitotane, which was the only adjuvant therapy in 55 of them. A method consisting of quickly increasing mitotane doses, beginning with 1.5-2.0 g daily, was used. For patients with localized disease the daily doses did not exceed 4.0 g. For patients with regional and metastatic disease the daily mitotane doses were increased every 5-7 days up to 8.0-10.0 g for two weeks and were

then gradually reduced. For long-term treatment a daily dose of 4.0 to 5.0 g was given during the first year, 3.0-4.0 g during the 2nd and 3rd year and 1.5-3.0 g during the next two years. In cases misdiagnosed at the time of surgery, the dose of mitotane was increased to 8.0-10.0 g daily, with the appearance of metastases or regional recurrence. Thirty-two patients received mitotane immediately after surgery, and 27 patients 2 to 15 months after the operation. One male patient referred to our department two years after removal of the carcinoma, with a recurrent tumor progressing during gamma-interferon administration and six cycles of chemotherapy, received mitotane at doses of 8.0-10.0 g daily for 3 months. The subsequent long-term doses ranged from 5.0 to 6.0 g a day. In another male patient, referred to our department five years after right adrenocortical carcinoma and metastatic prostate gland resection, the hormonal signs of left adrenal carcinoma appeared six months later. Mitotane treatment was administered immediately after left adrenal carcinoma removal. Cytostatic drugs were administered to nine patients (see Table 2), simultaneously with mitotane therapy in six of them. All patients treated with mitotane simultaneously received replacement therapy, hydrocortisone (30 to 50 mg daily) + prednisolone (5 to 10 mg daily) and fludrocortisone (0.1 to 0.15 mg daily). The doses of hydrocortisone were gradually reduced after mitotane withdrawal.

Serum mitotane concentrations were measured in the laboratory of the Child Health Center, Warsaw (by M. Filipek), in patients with regional or distant disease. Values ranging from 15 to 25 µg/ml were considered as active mitotane levels. In the last year, the plasma levels of mitotane and its metabolites (o,p'-DDA and o,p'-DDE) were determined at the Norwegian Radium Hospital, Department of Clinical Pharmacology (Oslo, Norway) by A. Andersen and D.J. Warren (6).

Group II included 22 women, 22-57 years old, with adrenal hyperfunction of non-malignant etiology. Sixteen patients (12 patients with Cushing's syndrome, three with an adrenal adenoma and one with nodular hyperplasia) received mitotane in short cycles (3-6 weeks) as pre-treatment before surgery. Six patients (four patients with Cushing's disease and two women with ectopic ACTH syndrome) have been treated with mitotane for much longer courses (ranging from three months to three years) because of poor tolerance or ineffectiveness of other anti-adrenal drugs (14,15). The daily mitotane doses ranged from 2.0 to 4.0 g. During long-term therapy (1-3 years) the maintenance mitotane dose was 1.0-1.5 g daily. Only one patient with a concomitant severe *Alternaria alternata* (opportunistic) infection received higher doses of up to 6.0 g per day for five weeks (241 g, in total). No replacement therapy with hydrocortisone has been necessary in five patients. Hydrocortisone has been administered to one patient at the dose of 10 mg every morning, together with mitotane at the dose of 0.5 g daily, during the second year of treatment.

Results

The results of treatment of 76 patients with adrenocortical carcinoma are summarized in Table 2. There were 18 survivors in the group of 32 patients treated with mitotane immediately after surgery (56%). Three of them were classified as metastatic and three others as regional disease. One patient with regional disease survived nearly 10 years on mitotane therapy. Five patients in this group died because of diseases not related to adrenal carcinoma. In the group of patients to whom mitotane was administered with a

Table 1 - Staging of 82 cases of adrenocortical carcinoma.

	Localized	Regional	Metastatic
Total	23	12	47
Incidental (29)	8	7	14
Non-incidental (53)	15	5	33

delay there were six survivors at the time of summarizing the results (22%). Similarly, only one patient survived out of 8 who did not use mitotane. In the patient with carcinoma recurring during gamma-interferon administration and chemotherapy, treatment with mitotane resulted in the reduction of tumor size from 12 to 6 cm on CT (16).

The side effects of mitotane therapy included an increase in aminotransferase and alkaline phosphatase activity (6 patients) and a fall in the number of leukocytes, platelets or erythrocytes (5 patients). A transient reduction of mitotane dose with a simultaneous increase of prednisolone dose was sufficient to obtain improvement of laboratory results in most patients. Myasthenia due to a toxic influence on neuromuscular junctions was observed only in three women, requiring reduction of mitotane daily dose or even withdrawal of the drug (in one patient).

Pre-operative mitotane administration to patients with Cushing's syndrome of non-malignant origin resulted in partial remission of the disease with good tolerance of surgical treatment. During long-term mitotane therapy in six patients with severe Cushing's syndrome, complete remission was obtained. In one patient with Cushing's syndrome complicated by a systemic *Alternaria alternata* infection, general improvement has been achieved with fungal infection healing (17). No undesired effects of mitotane therapy were observed in these patients.

Table 2 - Results of treatment of 76 patients with adrenocortical carcinoma.

*Distant or regional disease. 5-FU, 5-Fluorouracil.

Method	No. of patients	Survival (months)	No. of survivors
Surgery	8 (5*)	1-314	1
Surgery + adjuvant therapy	66 (37*)	4-118	26
+ mitotane	55 (29*)	4-118	24
+ mitotane, 5-FU	4 (4*)	4-24	0
+ mitotane, cisplatin, etoposide	2 (2*)	6-86	2
+ cisplatin, etoposide	3 (3*)	12-20	0
+ radiotherapy	2 (1*)	5, 12	0
Mitotane	2 (2*)	6, 10	0

Discussion

In our Department of Endocrinology, mitotane has been used for the treatment of adrenocortical carcinoma for 33 years (18). In our experience, surgery followed by immediate mitotane administration is the method of choice for adrenocortical carcinoma therapy. We give this drug to all patients with microscopically proved adrenal carcinoma, irrespectively of staging at the time of surgery because we have found that false-positive classification (untrue diagnosis of localized disease) has not been infrequent. According to Folkman's theory (19), we believe that dormant micrometastases may replicate after tumor removal due to a switch to the angiogenic phenotype in response to a decrease in plasma angiostatin concentrations. Mitotane administered as early as possible after the operation could prevent angiogenesis in the micrometastases and thus prevent carcinoma dissemination. The results of early mitotane administration for our series (56 *vs* 22% survival in the group with delayed treatment) seem to confirm this suggestion. Unfortunately, mitotane is not uniformly efficient in all cases of adrenocortical carcinoma, although it is possible that in most of them a delay in therapeutic intervention plays the most important role. What seems necessary in the interpretation of the results of therapy is analysis of the time when the therapy was introduced. In distant disease mitotane associated with cytostatic agents may be more effective (20).

Clinically silent adrenocortical carcinomas usually are found incidentally, mainly in the ultrasound scan. The detectability of the incidentally found malignant adrenal tumors could be increased by obligatory abdominal ultrasound scans (every two or three years, for example). In our series, 29 adrenocortical carcinomas were discovered incidentally (35.4% of 82 patients). In the group

of 451 patients referred to our department because of incidentally found adrenal masses the carcinomas appeared to be present in 6.7%.

The second type of mitotane use, i.e., in hypercorticism of non-malignant etiology, appeared to be beneficial to all treated patients. Mitotane seems to be the drug of choice in Cushing's disease associated with polycystic ovary syndrome because it does not stimulate androgen production as other inhibitors of steroidogenesis do.

The side effects of mitotane were rare in our material; only in one patient did we observe severe myasthenia, which forced us to withdraw the drug after one year of therapy. In our patients there were no features of neurotoxicity after long-term administration of high doses of mitotane exceeding 8.0 g per day (21). Nobody in our group of patients had vomiting or nausea, even with doses up to 10.0 g daily. We have administered slightly increased doses of hydrocortisone and prednisolone to prevent hypoadrenalism because both the above-mentioned symptoms may have been due to cortisol deficiency. In our experience, hydrocortisone associated with prednisolone and fludrocortisone seems to be better suited for replacement therapy than dexamethasone or prednisolone alone during mitotane administration. The determination of serum cortisol levels in our patients showed that mitotane did not change hydrocortisone absorption, although Robinson et al. (22) observed that the corticosteroids were cleared more rapidly from the circulation during mitotane administration.

Both high (23) and low (24) doses of mitotane have been recommended in the literature. It seems that the best method is to measure plasma mitotane concentration to choose the optimal mitotane dose.

It is not certain how long mitotane must be administered to patients without evident regional or distant invasion by adrenocortical carcinoma. I have adopted a period of four to five years and this period seems to be sufficient in most cases. However, the fact that one patient, not treated with mitotane, developed a left adrenocortical carcinoma in the sixth year after removal of a right adrenal carcinoma makes the five-year period of treatment questionable. Further observations are necessary to gain more knowledge about this matter.

We may summarize by saying that surgery associated with early mitotane administration is a method of choice for adrenocortical carcinoma treatment. In the distant stage simultaneous use of cisplatin and etoposide may have beneficial effects. Replacement therapy with slightly increased doses of hydrocortisone, fludrocortisone and prednisolone is necessary during mitotane administration. The side effects of mitotane are infrequent when the daily doses do not exceed 8.0-10.0 g.

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