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The Treatment of Adrenocortical Carcinoma with *o,p'*-DDD: Prognostic Simplications of Serum Level Monitoring*

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Abstract—*Thirty-four patients with adrenocortical carcinoma were treated with* o,p'*-DDD. Twenty-eight patients presented with metastases at entry, and spillage of tumour cells occurred at surgery in 6 other patients. Eight patients had objective tumour regression, of whom 7 had serum levels over* 14 μg/ml. *The* 3 *patients with a lasting remission had levels of* >15, >25, >25 μg/ml *respectively during prolonged periods. Increased survival times were found in the group of* 14 *patients with* o,p'*-DDD serum levels higher than* 14 μg/ml *when compared with patients not treated after discovery of metastases. In the patients with levels* ≤10 μg/ml *no therapeutic effect was seen. Levels of over* 20 μg/ml *are associated with symptoms of reversible neuromuscular toxicity. Monitoring of serum levels during treatment is mandatory. It is suggested that serum levels of about* 25 μg/ml *during longer periods may be curative.*

INTRODUCTION

THE AVERAGE survival time of untreated patients with adrenocortical cancer (A.C.) is 2.9 months after establishing the diagnosis [1]. Delayed commencement of a treatment regimen may be due to the rarity of the tumour [2] and the ensuing late discovery of an already advanced disease. Surgery is the treatment of choice in localized disease [1, 3–9]. However, even after radical surgery locoregional recurrence and metastases occur in 80% of the patients [3, 4].

Radiation has been applied to the post-operative tumour bed, inoperable tumours and metastases. Results, collected in large series, are poor [6, 10, 11]. In two centres, radiotherapy in 4 children [12] and in 7 adults [13] respectively showed, in addition to good palliative effects, lasting remission in at least one child [12] and one adult [13].

Cytotoxic drugs have shown little effect [14, 15]. Haq *et al.* [16] gave a review of the data published up to 1979. They found in their own material short-lived responses in 3 out of 12 cases. One patient treated with a combination of *o,p'*-DDD (1,1-dichloro-2,2-bis (*p*-chlorophenylethane))* and 5 fluorouracil showed a good response [17]. We found a 50% survival at 105 months of 11 patients with progressive metastatic disease after treatment with a combination of cyclophosfamide, adriamycin and cisplatinum [18].

o,p'-DDD has been in use since 1959 [19]. Large series of patients treated with *o,p'*-DDD, mostly from multi-institutional cooperative studies, have been reported, with varying results [5, 20, 21]. Temporary tumour regression was found in 20 out of 59 [5], 52 out of 85 [20] and 4 out of 14 [21] patients with this drug. In 11 isolated cases a complete remission of metastatic disease of more than 2 yr after the start of *o,p'*-DDD therapy is reported [17, 22–29].

Decrease in the excretion of 17-ketogenic steroids has been used as a criterion for tumour response. However, a change in cortisol metabolism by *o,p'*-DDD [30, 31] may be partly responsible for this decrease. In only a few

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*Proprietory name Lysodren (Calbiochem), Mitotane (Bristol-Myers).

patients are serum levels of *o,p'*-DDD mentioned. No relation between serum levels [32–34] and the results of treatment or of toxicity are described.

In this study the data of 34 patients treated with *o,p'*-DDD are presented, including 10 cases from an earlier publication [35]. The serum levels of *o,p'*-DDD are related to objective tumour response and signs and symptoms of toxicity. From this relationship a therapeutic range is derived.

MATERIALS AND METHODS

Thirty-four patients with histologically proven adrenocortical carcinoma received *o,p'*-DDD as sole chemotherapy. The average age was 46.6 yr (range 20–71 yr). Nineteen of these patients were females. Seventeen patients presented a clinical non-hormonal syndrome. The leading symptoms were pain, weight loss, fever and a palpable tumour. A clinical hormonal syndrome was found in the other 17 patients. A pure Cushing syndrome was found in 10, virilization in 6 and hyperaldosteronism in 1 patient.

Of the 32 patients who underwent surgery, 26 had measurable metastases at the start of the *o,p'*-DDD therapy. In the other 6 patients spillage was assumed to have occurred when the tumour capsule had ruptured during resection. We considered this as the onset of metastatic growth. In addition of the 32 patients mentioned, 2 patients with a measurable tumour load received *o,p'*-DDD without surgery. An additional 5 female and 3 male patients with metastatic disease who received no other specific tumour therapy after surgery served as a reference group. The average age in this group was 43.5 yr (range 8–68 yr). Three of these reference patients presented with a Cushing's syndrome, 2 with a virilizing syndrome and 3 had no clinical hormonal syndrome.

The tumour load at entry was estimated from palpation, X-ray pictures and liver-, bone- or CAT-scanning. Vitality of the patients at commencement of the *o,p'*-DDD therapy was estimated using the Karnofsky scale [36]. In 28 patients sufficient information was available for an evaluation of the adverse reactions of *o,p'*-DDD.

In order to maximize resorption the treatment was started with *o,p'*-DDD in milk-powder or in an oil emulsion [37], given in four equal oral doses per day. For maintenance therapy *o,p'*-DDD was given as tablets (Calbiochem or Bristol-Myers). Blood was taken at least 12 hr after the last dosage and serum levels of *o,p'*-DDD were determined according to Moolenaar *et al.* [38]. During treatment serum levels were measured at least once a month. The actuarial survival curves were calculated according to Kaplan and Meier [39]. The statistical analyses were carried out using the usual techniques as described by Armitage [40]. The plasma disappearance rates of dexamethasone and hydrocortisone were measured according to Peterson [41].

RESULTS

The localization of the metastases at the start of the therapy is shown in Table 1. The metastases were mostly observed in lung, liver, and bone. In the reference group metastases were localized in the liver (×4) and lungs (×3), and a local recurrence was found in 4 patients.

Table 2. Adverse reactions of o,p'*-DDD during therapy in 28 patients with adrenocortical cancer*

	No. of patients
Gastrointestinal ($n = 28$)	
Anorexia/nausea	26
Vomiting	23
Diarrhoea	19
Skin rash	9
Neuromuscular ($n = 18$)	
Confusion/sleepiness	18
Depression	6
Tremor	4
Dysarthria	5
Bradyphrenia	4
Ataxia	7
Visual disturbances	3
Leucopoenia	3

Table 1. Localization of metastases in 34 patients with adrenocortical cancer at the start of the o,p'*-DDD therapy*

	Liver	Lung	Bone	Lymph node	Skin	Local	Spilling
Liver	6	1	2	1	0	2	0
Lung		7	2	0	0	1	0
Bone			2	0	0	0	0
Lymph node				1	0	1	0
Skin					1	0	0
Local						1	0
Spilling							6

Side-effects were documented in 28 patients (see Table 2). Neuromuscular symptoms were seen in patients with serum levels of *o,p'*-DDD of over 20 μg/ml. Sleepiness and confusion were also found at lower levels. The symptoms worsened as serum levels increased. Only non-specific EEG-disturbances were found. In the 7 patients studied psychiatric abnormalities were observed in 3 patients, of whom 2 had a vital depression and 1 a psychosis at serum levels of over 30 μg/ml. Symptoms and EEG-abnormalities disappeared when serum levels decreased to 20 μg/ml. Other adverse reactions disappeared after interruption of the treatment and seemed to be independent of serum levels. Skin rash did not reappear after resumption of the treatment. The vehicle used in oral administration of *o,p'*-DDD seems to be of importance in the development of gastrointestinal side-effects, as is described in a previous study [37].

In the 34 patients who were treated with *o,p'*-DDD an objective tumour response was found in 8 cases (29%). Of these 8 patients 4 died, 8, 14, 19 and 34 months respectively after the start of the *o,p'*-DDD therapy (see Table 3). Four patients in this group are living: (I) one patient (No. 4) 32 months after the start of the *o,p'*-DDD treatment with regression of lung metastases and a seemingly stable disease till very recently. Now demonstrating symptoms of slowly progressive disease; (II) one patient (No. 7) 126 months after the start of the *o,p'*-DDD treatment with total regression of lung metastases and disease-free for 100 months; (III) one patient (No. 8, periods A and B) 165 months after the start of the first treatment. The first period (A) was concluded by resection of a lung metastasis followed by a disease-free period of 67 months. The second period (B) commenced by resection with spillage of an abdominal recurrence. After the operation *o,p'*-DDD treatment was re-established; (IV) one patient (No. 6) 47 months after the start of the *o,p'*-DDD treatment. A total regression proven with a second look of an inoperable local recurrence was observed. This patient has now been disease-free for a period of 23 months.

Table 3. Patients with objective tumour regression—survival after the start of o,p'*-DDD treatment*

Patient	Survival	Duration of regression	Treatment duration	Disease-free period
1	8	4	7	0
2	14	10	13	0
3	19	7	19	0
4	32‡	16	32	0
5	34	26	32	0
6	47‡	—	24	23
7	126‡	—	24	100
8 A*	98‡	14	31	67
B†	67‡	—	67	67

The duration of regression, treatment and disease-free period are expressed in months.

*Period of regression of lung metastases concluded with surgical intervention.

†Second period of *o,p'*-DDD treatment after non-radical surgery.

‡Living at the end of the study.

In 7 of the 8 patients with tumour regression *o,p'*-DDD serum levels of over 14 μg/ml were maintained for periods longer than 6 months. One patient did not attain serum levels higher than 10 μg/ml (patient 4, Table 3). In patient 8 tumour regression was seen in period (A) at serum levels below 10 μg/ml. In all three patients who showed total tumour regression, *o,p'*-DDD therapy was continued for at least 2 yr.

Of the 26 patients without objective tumour response, 6 had spillage of tumour cells at operation and developed metastases during *o,p'*-DDD therapy. From these 6 patients 4 attained *o,p'*-DDD serum levels of over 14 μg/ml for a period longer than 6 months. The other 20 patients, who had measurable tumour load, showed no objective response. Of these patients, 19 had *o,p'*-DDD serum levels lower than 10 10 μg/ml.

To evaluate the relation of the serum levels of *o,p'*-DDD with survival, the 34 patients were divided into two groups (A and B).

Group A: Patients who reached serum levels of over 14 μg/ml for a period of at least 6 months ($n = 14$). The average time taken to reach those levels was 2.8 ± 1.3 months. Seven patients had a hormonal syndrome.

Group B: Patients who did not reach serum levels of *o,p'*-DDD of over 10 μg/ml ($n = 20$). In this group 9 patients were treated less than 4 months. Ten patients had a hormonal syndrome.

Group C is the reference group ($n = 8$).

In group A, 11 patients died. Three patients are living and disease-free, with survival times of 47, 126, and 165 months respectively. The 50% survival time after the start of the *o,p'*-DDD therapy is 26.5 months.

In group B, 18 patients died. Two patients are living with survival times of 20 and 32 months after the start of the therapy: one patient after spillage seemingly disease-free and one with slow progressive disease. The 50% survival time is 4.5 months.

In group C the 50% survival time was 3 months after development of metastases. All patients died within 12 months.

Groups A and B were comparable in their chemical and histopathological parameters. Judged from the clinical parameters, the measurable tumour load was lower in group A than in

group B ($P < 0.01$). The Karnofsky scale was significantly better at entry in group A than in group B ($P < 0.01$). Karnofsky scale and tumour load in group C were significantly different at the start of the *o,p'*-DDD therapy from group A but not from group B.

Substantially decreased serum thyroxin levels were found in all 9 patients whose thyroid functions were measured during *o,p'*-DDD therapy. The resin uptake was raised, and TSH and ^{131}I neck uptake was normal. In 7 of 16 patients in whom serum cholesterol was measured a substantial hypercholesterolaemia was found during *o,p'*-DDD therapy. On paper electrophoresis lipoprotein patterns showed a Frederickson type IIa. In 6 of these 7 patients with hypercholesterolaemia the pre-treatment values were normal. Gynaecomastia and impotence developed during treatment in 6 of the 16 male patients.

Before steroid substitution was instituted, hypocorticism was documented during *o,p'*-DDD therapy in 6 patients. Clinical hypocorticism coincided with objective tumour response in 4 of these patients. During substitution with dexamethasone (1 mg/day) and fluorocortisone (0.1 mg/day) in a dosage scheme normally used in Addison's disease, signs and symptoms of hypocorticism were found in 4 patients. Single-sample ACTH levels measured in 3 of these patients were very high (198, 270 and 600 ng/l). These 4 patients showed low serum sodium and high serum potassium levels. Renin activity was measured several times in 1 patient and was found to be high (>20 ng AII/hr). In 3 patients a plasma $t_{½}$ of dexamethasone and hydrocortisone was measured before and after several months of treatment with *o,p'*-DDD. A mean decrease of 40% in the $t_{½}$ of dexamethasone was found (203 to 102, 195 to 117 and 188 to 148 min), while the plasma $t_{½}$ of hydrocortisone was increased at a mean of 40% (77 to 82, 70 to 109 and 61 to 103 min).

DISCUSSION

In this series of 34 patients the relationship between serum levels of *o,p'*-DDD and the therapeutic and toxic effects of the treatment were studied. Because of refusal of patient and/or physician, 8 additional patients received no further cytotoxic treatment after surgery when metastases developed. These patients were used as a reference group.

As criteria for the effectiveness of the drug, tumour regression and survival time were used. It appears that serum *o,p'*-DDD levels below 10 μg/ml have no significant effect on the 50% survival time (Fig. 1). Nine patients from group B ($n = 20$) used the drug for less than 4 months. This could be the reason why they did not reach adequate serum levels. When serum levels higher than 14 μg/ml were achieved (group A, $n = 14$), the 50% survival time was significantly longer ($P < 0.01$) than in groups B and C (Fig. 1).

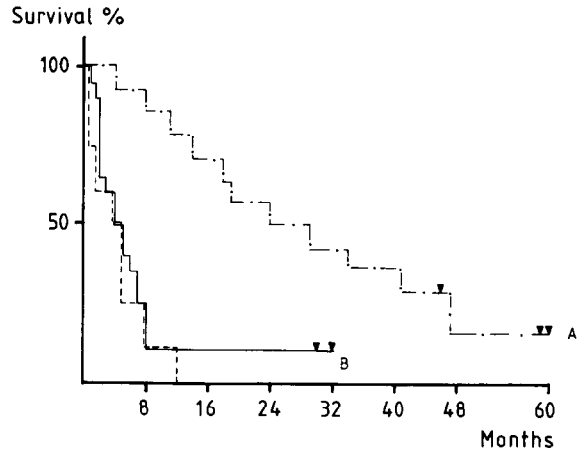

Fig. 1. Actuarial survival curves in months after the start of the o,p'-DDD therapy. Patient group A (n = 14), *o,p'-DDD serum levels* ≥14 μg/ml; *patient group B* (n = 20), *o,p'-DDD serum levels* <10 μg/ml; *patient group C* (n = 8), *reference group. Survival curve measured from the moment of detection of metastases.*

Seven of the 8 patients with objective tumour regression had serum levels of over 14 μg/ml. Of the 3 patients with lasting remissions, 2 had serum levels of over 25 μg/ml during longer periods, with peak levels of over 30 μg/ml. One patient had serum levels of about 15 μg/ml. Of the other 5 patients 4 had serum levels of over 14 μg/ml in the period of tumour regression. Of the 26 patients with progressive disease 21 never reached serum levels of over 10 μg/ml.

We conclude that, in general, serum levels of over 14 μg/ml must be reached for longer periods to obtain tumour regression, notwithstanding the fact that we found temporary tumour regression in 2 patients (Nos. 4 and 8A, Table 3) at serum levels of about 10 μg/ml. Higher levels are probably necessary to obtain a lasting remission, as can be seen in the 3 patients with proven lasting tumour remission. In the series reported here, 7 out of 14 patients who attained serum levels of >14 g/ml (group A) developed a remission which in 3 patients appears to be complete. Because of this, and because of the known malignancy and frequent recurrence of adrenal carcinoma after apparent radical surgery [3, 4], we advocate that all patients should be treated with *o,p'*-DDD after surgical intervention. This is also proposed by Greenberg and Marks [6] and Hoffman and Mattox [21].

In tumour therapy with cytostatic drugs the

best effects are generally seen when the tumour load is low. However, in one of our patients with a high tumour load a lasting remission is obtained (No. 6, Table 3).

At serum levels of over 20 μg/ml a gradual increase in neuromuscular toxicity occurs. At levels over 30 μg/ml intolerable symptoms appear. The strong increase in toxicity is in good correlation with the semi-log relationship between brain tissue levels of *o,p'*-DDD and serum levels, as has been reported in a previous study [42]. The decrease in serum thyroxine is caused by a change in the plasma transport of the hormone [43] and does not affect the free thyroxine levels. The cause of the hypercholesterolaemia is unknown. We found no relationship between plasma cholesterol and the therapeutic effect of *o,p'*-DDD as has been reported by Molnar *et al.* [44].

Drugs like fenytoine cause a decrease in the plasma half-life of dexamethasone and cortisol by an increased activity of the liver cytochrome-oxidase system [45, 46]. During *o,p'*-DDD treatment a decreased $t_{½}$ of dexamethasone but an increased $t_{½}$ of cortisol was found, suggesting that another mechanism must be involved. Increase in cortisol $t_{½}$ was also found by Southren *et al.* [47], but Kupfer *et al.* found a decreased $t_{½}$ of hydrocortisone [48]. The increased need of fluorocortisone in patients during *o,p'*-DDD therapy may be caused by a shortening of the plasma $t_{½}$ of this steroid, as was found for dexamethasone.

We conclude that in the therapy of patients with adrenocortical carcinoma with *o,p'*-DDD, no therapeutic effects can be expected at serum levels below 10 μg/ml. Serum levels must be raised as high as can be tolerated by the patients, at least to levels of 14 μg/ml. Serum levels of 25 μg/ml or higher are possibly better in view of our observation that 2 out of the 3 cured patients in this study achieved these levels. Whether it is possible to achieve this *o,p'*-DDD loading is obviously dependent on the dose-related side-effects of the drug.

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