Changes in neoplastic cell features and sensitivity to mitotane during mitotane-induced remission in a patient with recurrent, metastatic adrenocortical carcinoma

M Seki, K Nomura, D Hirohara, M Kanazawa, T Sawada, K Takasaki and H Demura

Department of Medicine, Institute of Clinical Endocrinology, School of Medicine, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

1Department of Pathology, Tokyo Women’s Medical University, Tokyo 162-8666, Japan

2Department of Surgery, Institute of Gastroenterology, Tokyo Women’s Medical University, Tokyo 162-8666, Japan

(Requests for offprints should be addressed to K Nomura; Email: nomura7@parkcity.ne.jp)

Abstract

A 58-year-old man had adrenocortical carcinoma in the right adrenal gland. The tumour secreted excessive cortisol and dehydroepiandrosterone-sulphate (DHEA-S), and had invaded the right hepatic lobe and vena cava. Eleven months after surgical tumour resection, the serum DHEA-S levels again increased. Local tumour recurrence and a metastasis was found in the lung. Eleven months after surgery chemotherapy with mitotane (o,p’-DDD) was initiated. Twelve weeks of mitotane reduced serum DHEA-S levels and caused these tumours to disappear. The patient was then treated with low-dose mitotane (1.5-2.0 g/day) for 2 years. Serum levels of mitotane remained at less than 10 µg/ml. Although such low serum levels of mitotane and delayed initiation of mitotane after surgery have been proposed to weaken the antineoplastic effect of mitotane, the patient had a remission for 2 years. However, there was then local re-recurrence with an increase in serum DHEA-S and death 4 months later. The histological features of neoplastic cells were quite different comparing tumour resected at surgery and tumour at autopsy. The latter had more frequent mitotic nuclei. This tumour was initially sensitive to mitotane, but later became insensitive.

Introduction

Adrenocortical carcinoma is a rare disease whose incidence has been reported to be approximately two persons per million a year (Hutter & Kayhoe 1966a). Surgery to remove all the tumour is the only reliable therapy (Venkatesh et al. 1989, Pomier & Brennan 1992, Søreide et al. 1992). Most patients, however, were found to have metastases of stage 3 or 4 which limited the surgical therapy (Cohn et al. 1986, Wooten & King 1993). Mitotane (o,p’-DDD) is the drug of choice for patients with inoperable, recurrent, and/or metastatic tumour. Although significant improvements were reported initially with mitotane (Hutter & Kayhoe 1966b, Lubitz et al. 1973, Jarabak & Rice 1981, Schteingart et al. 1982, Dickstein et al. 1998), later studies have suggested that mitotane was less effective (Boide et al. 1989, Luton et al. 1990, Vassilopoulou-Sellin et al. 1993). Serum drug levels were found to exceed 14 µg/ml in patients with successful tumour regression (Boven et al. 1984, Van Slooten et al. 1984, Haak et al. 1990, 1994). Longer survival was documented for patients medicated immediately after aggressive surgical therapy (Kasperlik-Zaluska et al. 1995). We present a patient with recurrent, metastatic adrenocortical carcinoma who had been treated with a low dose of mitotane for 2 years.
A 58-year-old man was incidentally found in a computerized tomography (CT) examination to have a right adrenal tumour (12 x 9.5 x 13 cm) invading the right hepatic lobe and inferior vena cava (Fig. 1A). Although he did not appear Cushingoid, he had high cortisol levels with suppressed adrenocorticotrophin (ACTH), and high dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-S) levels (Table 1). Urinary 17-ketosteroid (17-KS) excretion was also high when compared with urinary 17-hydroxycorticosteroid (17-OHCS) excretion. Serum oestrogen, which influences the SHBG (sex hormone binding globulin) and CBG (corticosteroid binding globulin), was not measured. There was no evidence of metastases. The tumour was resected, including the right hepatic lobe and part of the vena cava, in March 1995 (Fig. 1B). Histological examination was consistent with adrenocortical carcinoma (Fig. 2A). Plasma DHEA-S returned to the normal range and cortisol was low. The patient received hydrocortisone until August 1995. In February 1996, his DHEA-S level increased again. Computerized tomography examination revealed local tumour recurrence (5.5 x 5.5 x 8 cm) (Fig. 3A) and a solitary nodule (2.5 x 2 cm) in the right lung (Fig. 3C). He was diagnosed with recurrent and metastatic tumour 11 months after surgery. Histological examination was consistent with adrenocortical carcinoma (Fig. 2A). Plasma DHEA-S returned to the normal range and cortisol was low. The patient received hydrocortisone until August 1995. In February 1996, his DHEA-S level increased again. Computerized tomography examination revealed local tumour recurrence (5.5 x 5.5 x 8 cm) (Fig. 3A) and a solitary nodule (2.5 x 2 cm) in the right lung (Fig. 3C). He was diagnosed with recurrent and metastatic tumour 11 months after surgery. Chemothepany with mitotane, which was micronized and mixed with cellulose acetylphthalate, was initiated in April 1996, initially at 1.5 g/day and gradually increased to 6 g/day at maximum (Fig. 4). Serum mitotane levels were measured by gas chromatography as described in the Materials and methods section, and found to be changed according to the dosages used (Fig. 4). The serum levels remained below 9.2 mg/ml. After 12 weeks of mitotane, the metastatic tumour in the lung and the local recurrence disappeared (Fig. 3B and D). Plasma DHEA-S decreased to an undetectable level, and ACTH increased. These findings suggested that mitotane induced tumour regression with inhibition of adrenal steroidogenesis. After that, the patient was treated with low-dose mitotane (1.5-2.0 g/day) and with hydrocortisone (or dexamethasone). No metastases or recurrence were observed until April 1998. Routine laboratory data were normal except for high levels of gamma glutamyl transferase (γ-GTP). Although γ-GTP appeared to reflect the adverse effect of mitotane, the patient agreed to continue medication unless side-effects become severe. Serum cholesterol has been reported to be increased by mitotane, but remained rather low (3.21-4.45 mmol/l) in this patient. Serum mitotane concentration was measured several times, and was 9.2 µg/ml at maximum (Fig. 4). In April 1998, serum DHEA-S increased abruptly and CT examination revealed local tumour recurrence. Although the dose of mitotane was increased, direct tumour invasion to the retroperitoneum and rapid haematogenous metastases in the right kidney and the remaining liver accelerated during the last 3 months. Tumour thrombus in the inferior vena cava caused severe oedema of the lower limbs and ascites. Finally, in August 1998, rupture of a haematogenous metastases in the liver caused death. Autopsy and pathological examination was permitted. Morphology of the carcinoma cells was different from that in 1995 (Fig. 2B). In particular, mitotic nuclei were more prominent. In the region of the previous case, the proportion of mitotic figures was higher.
Materials and methods

Serum mitotane concentrations were determined based on methods described by Moolenaar et al. (1997) with minor modifications at the Hoechst Marion Roussel laboratory in Japan. Briefly, to 0.5 ml serum, 5 ml diethyl ether and 0.1 ml internal standard solution (80.0 µg/ml nervonic acid methyl ester) were added and the mixture was vortexed, followed by freezing at −20 °C. A diethyl ether layer was recovered, evaporated, and reconstituted with 0.1 ml chloroform to be injected into the gas chromatograph (Hewlett Packard HP-5890 series II equipped with FID and DB-23 column (J & W Scientific, Folxam, CA, USA)). Plasma for drug monitoring was taken in the morning, 2-3 h after drug administration.

Discussion

To obtain the best antitumour effect of mitotane, monitoring of the serum level, and immediate medication after aggressive tumour resections (including distant metastases) have been proposed. The effect of mitotane may not be wholly related to tumour steroidogenicity (Hutter & Kayhoe 1966b, Schteingart et al. 1982, Dickstein et al. 1998).

Van Slooten et al. (1984) reported that seven of eight patients with tumour regression had serum mitotane levels exceeding 14 µg/ml, while 19 of 20 patients without tumour regression had serum mitotane levels below 14 µg/ml. These findings suggested target mitotane serum level above 14 µg/ml. Haak et al. (1994) studied 62 patients...
and reported that mitotane treatment resulting in low serum levels (<14 µg/ml) was ineffective. To achieve such serum levels, mitotane was given starting with a dose of 4-8 g per day, and increased gradually (Van Slooten et al. 1984). Daily doses between 3 and 5 g have been used for long-term treatment in most patients (Van Slooten et al. 1984, Haak et al. 1994, Kasperlik-Zaluska et al. 1995). Higher doses such as 4-16 g/day have been reported to be unacceptable to most patients because of major side-effects including CNS toxicity (Hutter & Kayhoe 1966b, 1972).

Figure 3 Chest and abdominal CT scans before and after mitotane therapy. (A) Abdominal CT scan in April 1996 at local recurrence. (B) Abdominal CT scan in July 1996, taken 12 weeks after mitotane treatment. The recurrent tumour disappeared. (C) Chest CT scan in July 1996 demonstrating a tumour metastasis in the right lower lung (arrow). (D) The lesion in the lung had disappeared by 12 weeks after mitotane treatment in April 1996. The scale bar has a length of 5 cm. The arrows indicate the tumour.

Figure 4 Medication and examination time course. Doses of steroids and mitotane, plasma DHEA-S and ACTH, and serum γ-GTP and mitotane levels are shown.
Haak et al. 1994). Compared with these reports, our dosages were relatively low, i.e. an initial and maximum dose of 6 g/day, followed by a maintenance dose of 1.5 g/day. The serum mitotane level remained below 10 mg/ml throughout treatment. Thus, the mitotane level may not have been the principal factor for tumour regression in our case. A recent report of the combination of carefully repeated removal of all tumorous lesions including metastases together with prophylactic use of low doses of mitotane allowed a long remission period (Dickstein et al. 1998).

Longer survival is anticipated in patients treated early for adrenocortical carcinoma (Streide et al. 1992). Adjuvant mitotane chemotherapy lengthened survival when initiated immediately after aggressive tumour resection. Ten of 13 patients treated by surgery and immediate long-term adjuvant mitotane administration survived, compared with among 15 given mitotane 3-15 months after surgery (Kasperlik-Zaluska et al. 1995). Others also reported good survival with immediate mitotane therapy after aggressive surgery (Schteingart et al. 1982). Although our patient was treated with mitotane 11 months after aggressive surgery, mitotane treatment was associated with successful tumour regression. Therefore, at that time, the tumour may have been very sensitive to mitotane.

Mitotane induced complete remission in this patient for 2 years. Metastatic tumour in the lung disappeared. Locally recurrent tumour also disappeared initially, but re-recurred after 2 years with a rapid growth rate. Histological examination (Fig. 2B) of re-recurrent tumour after treatment with mitotane showed increased numbers of mitoses and invasion of the tumour capsule. Thus, the tumour became resistant to mitotane.

Our case indicates the importance of tumour sensitivity to mitotane in treating adrenocortical carcinoma. The transformation to a more malignant phenotype, however, limited the antitumour effect of mitotane.

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References


