Japanese single-institution analysis of mitotane for patients with adrenocortical carcinoma

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Abstract. Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis. While mitotane is the only agent approved for ACC, clinical data are scarce, especially in the Asian population. We reviewed 10 patients with ACC who received mitotane as a single agent or in combination with other agents in our institution. Patient characteristics, clinical outcomes, and toxicities were analyzed. Mitotane was administered to 2 patients as an adjuvant therapy and to 8 patients for systemic control. In the latter 8 patients, 1 patient had locally advanced disease and 1 had metastatic disease at the time of initial diagnosis, whereas the other 6 patients experienced metastatic relapse at mitotane initiation. The administered regimen was mitotane alone in 7 patients, and mitotane plus cytotoxic chemotherapy in 3 patients. The initial daily mitotane dose was 3.0 g in 2 patients, 1.5 g in 7 patients, and 1.0 g in 1 patient. The median duration of treatment was 3.7 (range, 0.7–22.1) months. In 8 systemic cases, the median overall survival from chemotherapy initiation was 7.2 months, and only 1 patient survived over 1 year. The median interval from mitotane termination to death in systemic cases was 2.8 months, and the cause was progressive disease in 4 patients and toxicity (hallucination, mycobacteriosis, or liver injury) in 3 patients. As a second-line regimen, 2 systemic cases and 1 adjuvant case were enrolled in clinical trials. Our analysis exhibited extremely poor prognosis under mitotane-based regimens, and further treatment strategies are warranted to improve outcomes.

Key words: Adrenocortical carcinoma, Chemotherapy, Mitotane, Japanese cohort

ADRENOCORTICAL CARCINOMA (ACC) is a rare malignancy, and the estimated annual incidence is 0.5–2.0 per million people per year [1, 2]. The peak age of onset is 40–50 years, although patients can develop ACC regardless of age [3]. While most ACC cases occur sporadically, several hereditary syndromes such as Li-Fraumeni syndrome and multiple endocrine neoplasia type 1 are associated with onset in some cases [4, 5]. Conditions leading to excess hormones, including hypercortisolism, are observed in more than half of these patients [6]. The prognosis is heterogeneous depending on the clinical stage. According to a study based on the revised European Network for the Study of Adrenal Tumors (ENSAT) classification, the 5-year disease-specific survival rate was 82% for stage I, 61% for stage II, 50% for stage III, and 13% for stage IV [7]. Clinical behavior in metastatic cases is highly aggressive, and further treatment strategies are strongly warranted.

Mitotane is the only agent approved for inoperable advanced ACC by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), although there have been no randomized trials on mitotane alone [8]. In Japan, an application for the manufacture and sale of this agent was approved in 1983. Although it has been proposed that this agent can mechanically suppress the adrenal cortex with cellular destruction, the mechanism of action has not been fully elucidated [8]. Mitotane is used not only as a single agent but also in combination with other cytotoxic agents...
such as etoposide, doxorubicin, and cisplatin (EDP) [9]. As for advanced cases, clinicians consider various factors such as tumor burden, site of disease, pathological features, clinical symptoms, and patient performance status, and select mitotane alone or a mitotane combination regimen [10]. This agent is also adopted in adjuvant therapy following complete resection, and the application is individually judged depending on the ENSAT stage and pathological features (Ki-67 index) [10].

Mitotane has various unique toxicity profiles such as gastrointestinal symptoms, central nervous system disturbances, and adrenal insufficiency [11]. Moreover, this agent is metabolized in the liver and functionally enhances CYP3A4 activity [8]. It should be noted that mitotane itself is not pharmacologically active and it is its metabolites that have an adrenolytic effect. Therefore, drug interactions with other agents often become a practical problem. As there is little data in the Asian population regarding mitotane, we conducted a Japanese single-institution analysis of clinical efficacy and toxicity along with dose modification and treatment duration. In this study, we aimed to obtain referential information about the use of mitotane in daily practice.

Materials and Methods

We retrospectively reviewed the Cancer Institute Hospital of the Japanese Foundation for Cancer Research database of patients with pathologically proven ACC from 1987 to 2018. This study was reviewed and approved by the Institutional Review Board of the Japanese Foundation for Cancer Research and conducted in accordance with the precepts established by the Helsinki Declaration. Clinically suspected cases without pathological diagnosis were excluded, and only patients who received mitotane as a single agent or combination therapy in our institution proceeded to further analysis. Clinical data reviewed included sex, age at initial diagnosis, smoking/alcohol history, history of any cancer, family history of any cancer in a first-degree relative (FDR), primary site (right or left adrenal gland), longest tumor diameter, clinical stage (ENSAT stage) at initial diagnosis, disease status at relapse, existence of Cushingoïd features, serum levels of cortisol and dehydroepiandrosterone (DHEAS), level of plasma adrenocorticotropic hormone (ACTH), treatment approach (surgery or chemotherapy), chemotherapy regimen, and toxicity in relation to the agent. To evaluate the pathological features, hematoxylin and eosin-stained 4-μm sections of formalin-fixed paraffin-embedded tissue were used. The diagnosis of ACC was made according to the Weiss histopathologic system, which is the most commonly used method for assessing the likelihood of malignancy [12]. The pathological features of all available cases were reviewed by two experienced pathologists (Y.S. and K.I.). For immunohistochemistry for Ki-67/ Mib-1, sequential 4-μm sections were stained with a monoclonal antibody (1:200; clone: MIB-1; DAKO, Glostrup, Denmark). Moreover, we tried to collect information on the initial dose and subsequent dose modification of mitotane. The administration duration was calculated as the interval from mitotane initiation to the last administration date, and in patients who were transferred to another hospital and whose subsequent medical records were unavailable, the transfer day was described as the last day of administration. Overall survival (OS) was calculated as the interval from mitotane initiation to death or the last follow-up, and survival curves were estimated using the Kaplan–Meier method. Univariate analyses of risk factors for OS were performed using a Cox proportional hazards regression model. Effects were considered statistically significant if two-sided p-values were below 0.05. All statistical analyses were performed using EZR version 1.53 (Saitama Medical Center, Jichi Medical University), which is based on R and R commander (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/download.html) [13].

Results

Patient characteristics

Over a 30-year period, 17 patients were pathologically diagnosed with ACC. Among them, 4 patients who did not receive any chemotherapy, 1 who received chemotherapy without mitotane, and 2 who received a mitotane-based regimen in another hospital were excluded from the analysis. The clinical characteristics of the remaining 10 patients who received a mitotane-based regimen in our institution are summarized in Table 1. Detailed clinical data for each patient are listed in Table 2. The median patient age was 59.5 years (range, 48–71 years), and the percentage of patients aged <50 years was 30%. The left adrenal gland was the primary lesion site in 70% of the cases, and the median tumor diameter was 8.8 cm (range, 3.1–18.0 cm). According to the histological evaluation, 4 cases had a Weiss score of 4 and 5 cases had a score of 6. The Ki-67 index ranged between 10–50% (median 30%). The initial ENSAT stage was stage I in 1 patient, stage II in 5 patients, stage III in 1 patient, and stage IV in 1 patient. While 1 patient had locally advanced disease (ENSAT stage III) and 1 had metastatic disease (ENSAT stage IV) at the time of initial diagnosis, the other 6 patients experienced metastatic relapse during their clinical course. In the 6 patients with a metastatic relapse, the median interval from the initial diagnosis to the metastatic relapse, and
from the metastatic relapse to mitotane initiation, was 29.3 months (range, 6.5–114.5 months) and 8.5 months (range, 0.3–60.2 months), respectively. Three of the 6 patients with a metastatic or locally advanced relapse had previously undergone surgical resection of the relapsed lesion, with intervals of 26.2, 18.3, and 10.9 months between the surgery and the subsequent recurrence. The most common metastatic organs were the lung in 3 patients and the liver in 2. Elevated levels of cortisol, ACTH, and DHEAS at the time of mitotane initiation were detected in 40% (4/10), 20% (2/10), and 13% (1/8) of patients, respectively. According to the available data, 3 patients exhibited some Cushingoid feature including 2 patients with striking cortisol or DHEAS levels (ID-7, ID-8). The percentages of smokers and drinkers were 22% and 56%, respectively. Three (30%) patients had a history of any cancer, and four (50%) patients had a family history of cancer in an FDR. Patient ID-10 with a history of breast cancer and a family history of lung and uterine cancer harbored a mutation in \textit{BRCA1}, which is a homologous recombination repair gene. As part of the screening test in a clinical trial, genomic analysis in patient ID-10 was conducted using resected tumor specimens but not in blood samples, and it was unknown whether this patient was categorized as hereditary breast and ovarian cancer syndrome (HBOC).

### Detailed information about mitotane-based chemotherapy

Eight (80%) patients received mitotane for systemic control (7 for metastatic disease and 1 for locally advanced disease), and two received the agent as adjuvant therapy without residual lesion. Regimen selection was based on the clinician’s choice, and mitotane combination regimens were used primarily for treating clinically aggressive cases. Mitotane was administered as a single agent in 7 patients, and in combination with EDP in 2 patients or carboplatin/paclitaxel in 1 patient (Table 3). The initial mitotane daily dose was 3.0 g in 1 patient, 1.5 g in 8 patients, and 1.0 g in 1 patient, and the maximum daily dose was 6.0 g in 1 patient, 4.5 g in 2 patients, and 1.5 g in 7 patients. The median initial dose and median maximum dose was 1.5 g, and dose modification from the initial dose was conducted in 5 cases (50%). The median treatment interval in the entire cohort was 3.7 months (range, 0.2–12.3 months), with a median interval of 3.7 months for systemic therapy and 5.0 months for adjuvant therapy. Mitotane was discontinued because of progressive disease (PD) in 4 patients and adverse events (hallucination, mycobacteriosis, or liver injury [elevated γ-GTP with grade 4, elevated alanine aminotransferase with grade 3, and elevated aspartate aminotransferase with grade 2]) in 3 patients.

### Clinical outcomes

In the 8 systemic cases, the median OS from mitotane initiation was 7.2 months, and only 1 patient survived over 1 year (1-year OS rate: 12.5%) (Fig. 1). There was no significant difference in OS between cases with a Ki-67 index ≥40% and those with a Ki-67 index <40% ($p = 0.31$), or between cases with a Weiss score of 6 and those with a Weiss score of 4 ($p = 0.45$). When calculated from initial diagnosis, the median OS was 37.5 months. None of the patients achieved a shrinkage of the tumor volume on radiology (Table 3). The median interval from mitotane termination to death in systemic cases was 2.8 months. However, 2 adjuvant cases survived for approximately 3 years or more. Following confirmed PD, two systemic cases (ID-3, ID-5) and one adjuvant case (ID-10) were enrolled in clinical trials as second-line regimens. After mitotane termination, the two patients with systemic disease (ID-3 and ID-5) developed hypertension, and multiple classes of antihypertensive agents (calcium channel blockers, alpha blockers and angiotensin II receptor blockers for ID-3; calcium channel blockers and thiazide diuretics for ID-5) were required to control the hypertension.

| Table 1  | Clinical characteristics of 10 adrenocortical carcinoma cases who received mitotane |
|----------|----------------------------------------------------------------------------------|
| Variables | Number (%)                                                                 |
| Age      | Median 59.5 (48–71)                                                             |
| Sex      | Male 3 (30%) Male 7 (70%)                                                      |
| Primary site |                                      |
| Right adrenal gland | 3 (30%) |
| Left adrenal gland  | 7 (70%)                             |
| Tumor diameter (cm) | Median 8.8 (3.1–18.0)             |
| ENSAT stage at initial diagnosis |                      |
| I        | 1 (13%)                                                                 |
| II       | 5 (63%)                                                                 |
| III      | 1 (13%)                                                                 |
| IV       | 1 (13%)                                                                 |
| Smoking  | Yes 2 (22%)                                                                    |
| Alcohol  | Yes 5 (56%)                                                                     |
| History of any cancer | 3 (30%)                                     |
| Family history of any cancer with FDR | 4 (50%)                              |

ACC, adrenocortical carcinoma; ENSAT, European Network for the Study of Adrenal Tumors; FDR, first-degree relative.

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Table 2  Clinical data of patients who received mitotane

| Patient ID | Sex | Age at initial diagnosis (years) | Primary site | Lesions at mitotane initiation | Tumor diameter (cm) | Weil score | Ki-67 index | ENSAT stage at initial diagnosis | Cushingoid feature | Serum cortisol level before treatment (µg/dL) | Plasma ACTH level before treatment (pg/mL) | Serum DHEAS level before treatment (µg/dL) | Smoking (BI) | Alcohol | History of any cancer | Family history of any cancer with FDR |
|------------|-----|---------------------------------|--------------|-------------------------------|---------------------|------------|-------------|----------------------------------|-------------------|----------------------------------------|-------------------------------------------|---------------------------------------|------------|---------|----------------------|------------------------|
| 1          | F   | 48                              | Left adrenal | Pericardium, pleural effusion | 12.6                | 6          | 20%         | 2                                | None              | 22.9                                   | 88.5                                     | NA                                    | 0          | NO      | None                 | NA                     |
| 2          | F   | 48                              | Right adrenal| Mediastinum                   | NA                  | 4          | 40%         | NA                               | None              | 20.1                                   | 5.0>                                    | NA                                    | 560        | NO      | None                | Uterine cancer (mother) |
| 3          | M   | 48                              | Left adrenal | Lung, pleural, hilar LN       | 7.2                 | 4          | 30%         | 2                                | None              | 9.7                                    | 16.7                                     | 113                                   | 300        | YES     | None                | Liver cancer, breast cancer |
| 4          | F   | 54                              | Left adrenal | Lung                          | 7.0                 | 6          | 40%         | 2                                | None              | 11.2                                   | 38.5                                     | 52                                    | 0          | YES     | None                | Colorectal cancer (mother 70 years) |
| 5          | F   | 58                              | Left adrenal | Paraortic LN, subclavian LN   | 8.6                 | 6          | 50%         | 3                                | HT               | 10.9                                   | 110                                      | 214                                   | 0          | NO      | None                | None                   |
| 6          | M   | 61                              | Left adrenal | Liver                         | 12.0                | 6          | 50%         | 4                                | None              | 13.7                                   | 21.1                                     | 745                                   | 0          | YES     | None                | None                   |
| 7          | M   | 62                              | Right adrenal| Lung                          | 3.1                 | 4          | 10%         | 1                                | HT, palpitation, lower limb edema, moon face | 67.6                  | 7.1                                      | 360                                 | 0          | YES     | Kidney cancer, colorectal cancer | Esophageal cancer (mother 62 years), breast cancer (sister 62 years) |
| 8          | F   | 71                              | Left adrenal | Liver                         | NA                  | NA         | NA          | NA                               | HT, night sweat  | 27.7                                   | 10                                      | 3,200                                 | 0          | NO      | None                | None                   |
| 9          | F   | 69                              | Right adrenal| None                          | 9.0                 | 6          | 20%         | 2                                | None              | 11.4                                   | 47.3                                     | 3                                     | NA         | NA      | None                | Lung cancer (brother 60 years), uterine cancer (sister 47 years) |
| 10         | F   | 69                              | Left adrenal | None                          | 18.0                | 4          | 10%         | 2                                | None              | 14.1                                   | 22.1                                     | 75                                    | 0          | YES     | Breast cancer       | None                   |

ENSAT, European Network for the Study of Adrenal Tumors; BI, Brinkman Index; FDR, first-degree relative; F, female; M, male; NA, not available; LN, lymph nodes; HT, hypertension.

Reference ranges: 4.0–18.3 µg/dL for cortisol, 9–52 pg/mL for ACTH, and 50–1,000 µg/dL for dehydroepiandrosterone sulfate.
This study showed remarkable features in Japanese patients with ACC. First, 6 out of 8 cases with systemic mitotane experienced metastatic relapse after surgical resection. Ayala-Ramirez et al. reviewed 330 ACC cases at the University of Texas MD Anderson Cancer Center and showed that distant metastasis was observed in 66% of the cases during follow-up [14]. Clinicians should carefully monitor the possibility of subsequent relapse even after surgery. Second, our cases had a relatively high proportion of a history of any cancer (30%) and family history with an FDR of any cancer (50%). According to the aforementioned study, the proportion of patients with any cancer history was 12%, and 2% and 0.3% of the patients were diagnosed with Li-Fraumeni syndrome and multiple endocrine neoplasia type 1, respectively [14]. Third, 3 patients with metastatic or locally advanced relapse initially received surgery but not chemotherapy and experienced a considerable relapse-free period. Widespread metastases are not amenable to salvage resection. Conversely, cases with an interval of more than 12 months between the primary resection and the clinical relapse, and a single metastatic

**Table 3** Detailed information of mitotane-based regimens

| Patient ID | Regimen                      | Purpose of treatment | Mitotane dose at initiation | Maximum mitotane dose | Mitotane dose at termination | Best radiological response | Treatment duration | Cause of termination | Second-line regimen | OS from treatment initiation | OS status |
|------------|------------------------------|----------------------|-----------------------------|-----------------------|-----------------------------|---------------------------|---------------------|---------------------|------------------------|-----------------------------|------------|
| 1          | Oral CY followed by mitotane | Systemic            | 1.5 g                       | 4.5 g                 | 1.0 g                       | NA                        | 3.2 months         | NA (hospital transfer) | None                   | 3.9 months                  | Dead       |
| 2          | Mitotane                     | Systemic            | 3.0 g                       | 6.0 g                 | 3.0 g                       | PD                        | 5.7 months         | NA (hospital transfer) | None                   | 7.5 months                  | Dead       |
| 3          | EDP-mitotane                 | Systemic            | 1.5 g                       | 1.5 g                 | 1.5 g                       | PD                        | 4.6 months         | PD                  | Novel agent            | 8.2 months                  | Dead       |
| 4          | EDP-mitotane                 | Systemic            | 1.5 g                       | 4.5 g                 | 3.0 g                       | SD                        | 12.3 months        | PD                  | None                   | 34.4 months                 | Dead       |
| 5          | Mitotane                     | Systemic            | 1.5 g                       | 1.5 g                 | 1.5 g                       | PD                        | 1.4 months         | PD                  | Novel agent            | 8.5 months                  | Dead       |
| 6          | Mitotane                     | Systemic            | 1.5 g                       | 1.5 g                 | 1.5 g                       | NA                        | 0.4 months         | NA (hospital transfer) | None                   | 1.7 months                  | Dead       |
| 7          | Mitotane                     | Systemic            | 1.5 g                       | 1.5 g                 | 1.5 g                       | NA                        | 0.2 months         | Hallucination        | None                   | 3.6 months                  | Dead       |
| 8          | CBDCA/PTX-mitotane           | Systemic            | 1.0 g                       | 1.5 g                 | 1.5 g                       | PD                        | 4.6 months         | PD                  | None                   | 6.9 months                  | Dead       |
| 9          | Mitotane                     | Adjuvant            | 1.5 g                       | 1.5 g                 | 1.0 g                       | Excluded                  | 7.9 months         | Mycobacteriosis      | None                   | 35.9 months                 | Alive      |
| 10         | Mitotane                     | Adjuvant            | 1.5 g                       | 1.5 g                 | 1.5 g                       | Excluded                  | 2.1 months         | Liver injury         | Novel agent            | 119.1 months                | Alive      |

OS, overall survival; CY, cyclophosphamide; EDP, etoposide, doxorubicin and cisplatin; CBDCA, carboplatin; PTX, paclitaxel; NA, not available; PD, progressive disease; SD, stable disease.

**Fig. 1** OS data in patients who received mitotane for systemic control. OS was calculated from mitotane initiation. OS, overall survival

**Discussion**

This study showed remarkable features in Japanese patients with ACC. First, 6 out of 8 cases with systemic mitotane experienced metastatic relapse after surgical resection. Ayala-Ramirez et al. reviewed 330 ACC cases at the University of Texas MD Anderson Cancer Center and showed that distant metastasis was observed in 66% of the cases during follow-up [14]. Clinicians should carefully monitor the possibility of subsequent relapse even after surgery. Second, our cases had a relatively high proportion of a history of any cancer (30%) and family history with an FDR of any cancer (50%). According to the aforementioned study, the proportion of patients with any cancer history was 12%, and 2% and 0.3% of the patients were diagnosed with Li-Fraumeni syndrome and multiple endocrine neoplasia type 1, respectively [14]. Third, 3 patients with metastatic or locally advanced relapse initially received surgery but not chemotherapy and experienced a considerable relapse-free period. Widespread metastases are not amenable to salvage resection. Conversely, cases with an interval of more than 12 months between the primary resection and the clinical relapse, and a single metastatic...
 Patients with ACC who received a mitotane-based regimen had an extremely poor prognosis. The median OS of 8 patients who received mitotane for systemic control was only approximately 7 months. Similarly, 2 larger-scaled studies including 85 and 330 metastatic cases in the United States exhibited a short OS (median OS: 10.8 months and 9.1 months, respectively) with mitotane [14, 15]. Because of the rarity of ACC, clinical data from Japan are extremely limited. Nishida et al. conducted a retrospective analysis of 14 ACC cases over 34 years [16]. In their study, mitotane was administered to 7 patients and mitotane plus EDP to 3 patients for disease recurrence and metastasis, respectively. The average OS from surgery was 108 months in patients with stage II–III and only 2 months in those with stage IV cancer. In terms of actual dose and period, the median daily mitotane dose was 3.0 g (range, 0.5–12.0 g), and the median duration was 11 months. The Ki-67 index is regarded as a useful tool to estimate subsequent clinical behaviors. Regarding resected cases, Beuschlein et al. reported that patients with a Ki-67 index <10%, 10–19%, and >20% all significantly differed in terms of OS [17]. The ESMO guidelines recommend adjuvant mitotane after complete resection for patients with a Ki-67 index >10% [10]. However, its impact on advanced cases has not been determined [18]. In our analysis, 6 of 7 patients with advanced disease had a Ki-67 index ≥20%, which might be related to their poor prognosis. The Weiss score was 4 or 6 in all available cases, which fulfills the diagnosis of adrenocortical malignancy [12].

Although there is no standard administration dose or schedule of mitotane, dose modification targeting blood levels between 14 μg/mL and 20 μg/mL is generally recommended [8]. Fay et al. proposed an initial daily dose of 0.5 g and an increased dose of 0.5 g per week [8]. Previous studies showed that cases with a mitotane serum level ≥14 mg/L harbored a better OS than those with a lower level [14, 19]. Owing to the lack of insurance approval, monitoring is not currently pervasive in Japan. Therefore, we cannot ignore selection bias, and further analysis is required to assess the clinical benefit more rigorously. Second, owing to the retrospective nature, detailed
information about hormone hypersecretion symptoms or any side effect was unavailable, and the time of image evaluation, such as computed tomography and blood hormonal level monitoring, was heterogeneous in the respective cases. Third, the mitotane administration interval was too short to assess radiological response in many cases. Finally, comprehensive genomic analysis was not conducted in this study, and elucidating pathophysiological associations with hereditary syndromes or identifying all druggable targets was impossible. In conclusion, our analysis exhibited unsatisfactory prognosis under a mitotane-based regimen. The outcomes might partly reflect the clinical practice in which mitotane administration is not stopped even in terminal care. Further treatment strategies including novel agents are warranted in the future. Our clinical data in the Asian cohort potentially contribute to future meta-analyses.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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