Systemic chemotherapy for adrenocortical carcinoma: comparative responses to conventional first-line therapies

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The objective of this study was to evaluate and compare the efficacies of conventional first-line chemotherapies for adrenocortical carcinoma. We reviewed the records of adult patients (≥ 17 years) who had received first-line systemic chemotherapy with serial pretreatment and posttreatment radiologic staging studies in our institution between 1980 and 2000. Overall survival (OS) and time to progression (TTP) for different treatment groups were determined using the Kaplan–Meier method and were compared using the log-rank test. Univariate and multivariate models were fitted to different subsets of patients for OS and TTP and used to calculate hazard ratios (HRs) with 95% confidence intervals. We identified 224 patients with a diagnosis of adrenocortical carcinoma, 57 of whom met the inclusion criteria for further study. Chemotherapy groups included: mitotane ($n=12$), platinum and etoposide ($n=16$), mitotane with platinum and etoposide ($n=11$), mitotane and other cytotoxics ($n=5$), platinum and etoposide with other cytotoxics ($n=3$), and other miscellaneous cytotoxics ($n=10$). No statistically significant differences in OS ($P=0.31$) were noted among the treatment groups, but there was a statistically significant difference in TTP ($P=0.02$) favoring mitotane alone (TTP = 6.24 months; 95% confidence interval, 3.58–32.13). Multivariate analysis was most notable for a significantly greater OS (HR = 0.49, $P=0.04$) and TTP (HR = 0.3, $P=0.01$) associated with peritoneal metastases. Our analysis revealed no clear advantage for any single agent or combination over any of the other conventional frontline chemotherapeutic choices for adrenocortical carcinoma. Novel agents are thus sorely needed in the treatment of this aggressive cancer.
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Introduction

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy affecting 1–2 per million persons per year [1]. Approximately half of all ACCs are functional, and diagnosis may follow a rapid and progressive clinical presentation of hormone excess [2]. The remaining ACCs are typically diagnosed from the mass effect of the primary tumor or from the presence of metastases; most ACCs are greater than 10 cm in diameter and up to one-third have metastasized by the time of diagnosis [3]. The actuarial 5-year survival for patients with ACC at all stages is 60% [4]. However, advanced disease (characterized by local invasion, lymph node involvement, or distant spread) is associated with poor outcomes; the 5-year survival for patients with stage III ACC is 24% and falls to a dismal less than 7% in stage IV disease [5]. The best opportunity for cure is complete operative removal of the cancer, but frequent advanced disease at presentation often precludes any success with total tumor resection. In patients who do not undergo complete surgical resection at diagnosis, 5-year survival can be as low as 5% [6].

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Systemic chemotherapy is the primary option in cases where surgery is incomplete or contraindicated. However, information on the efficacy of the different chemotherapies for ACC has been limited by the rare occurrence of this cancer, and current best practices have emerged primarily on the basis of results from small series and anecdotal experience. A cumulative body of experience is necessary to help guide therapeutic decisions for this rare malignancy. Toward that end, we reviewed the files of patients who received frontline systemic therapy for ACC at our institution and report our findings of outcomes with various chemotherapeutic agents and combinations.

Methods

We searched our Tumor Registry database for all patients with a diagnosis of ACC seen there between 1980 and 2000. We chose 1980 as the search starting date to coincide with the standardized use of computerized tomography in cancer diagnosis and follow-up at our institution; we chose 2000 as the search end date to allow for up to 5 years of continued clinical care to ensure accurate and meaningful estimates of survival.

The files of adult patients (age ≥ 17 years) with a diagnosis of ACC who had received first-line systemic chemotherapy were selected for further review. We included only patients who had radiologically measurable disease at the start of medical (nonadjuvant) therapy and who underwent consistent serial computerized tomography or magnetic resonance imaging to evaluate response to treatment. Patients without a confirmed diagnosis, serial imaging studies, or adequate follow-up were excluded from our study. In each case, we compared radiologic tumor burden before and after a given drug or drug combination. Applying modified response evaluation criteria in solid tumors [7], we categorized posttreatment imaging studies as showing: (a) a decrease in tumor burden (partial or complete response), (b) no change in tumor burden (stable disease), or (c) an increase in tumor burden (progressive disease). Patients who did not have posttreatment imaging studies owing to rapid clinical deterioration were considered to have progressive disease.

Over the defined study interval, the most commonly used systemic agents for ACC included mitotane, platinum-based drugs, and etoposide. To better evaluate their efficacy, we grouped these treatment choices as: (i) platinum and etoposide; (ii) platinum, etoposide, and mitotane; (iii) platinum, etoposide, and other cytotoxic agents; (iv) mitotane; (v) mitotane and other cytotoxic agents (not including combination platinum and etoposide); and (vi) miscellaneous other cytotoxic agents (composed of drugs or combinations that did not fall within any of the other categories).

Overall survival (OS) was measured from the date of the first treatment with systemic chemotherapy to the date of the patient's death; in cases where death was not confirmed in the medical record, we used the online Social Security Death Index (*http://ssdi.rootsweb.com/*) to determine date of death. Time to progression (TTP) was measured from the date of treatment to the date of cancer progression. Time to treatment (TTT) was measured from the date of diagnosis to the date of first treatment with systemic chemotherapy.

The Kaplan–Meier method was used to estimate survival distributions, and the log-rank test was used to compare survival distributions among the various treatment groups. Univariate and multivariate Cox models were fitted to different subsets of treated patients for OS and TTP. The multivariate model was fitted using factors that were statistically significant ($P < 0.05$) in the univariate model. All the statistical analyses were performed using SAS 9.1 (SAS, Cary, North Carolina, USA) and S-PLUS 6.1 (Lucent 5 Technologies, Inc., Murray Hill, New Jersey, USA).

Results

Of 224 patients with a diagnosis of ACC who received their care at our institution between 1980 and 2000, 57 patients met the criteria for inclusion into our study (Table 1). According to the staging system proposed by Lee *et al.* [8], 52 study patients had stage IV disease at the time of medical treatment (presence of metastases), and the remaining five had stage III (local invasion, direct extension into the inferior vena cava, or regional lymph node involvement). All 57 patients were screened for hypercortisolemia, and excess cortisol secretion was biochemically confirmed in approximately 40% of the cases. Twenty-five study patients (44%) had metastases at the time of diagnosis, and 40 patients (70%) had had at least one surgical resection of their cancer before receiving systemic therapy. The most common sites of distant metastases at the start of treatment in our patients were the lungs (54%), liver (47%), peritoneum (26%), and bone (11%). At the start of chemotherapy, 17 patients had primary unresected disease in the adrenal gland (30%) and 11 patients had disease recurrence in the adrenal bed (19%). Of 57 patients, 15 (26%) were alive 5 years after the diagnosis of ACC, 14 of whom had stage IV disease at the time of systemic chemotherapy.

Platinum and etoposide

Sixteen patients in our study received combination platinum (cisplatin) and etoposide as frontline chemotherapy for ACC, the mean TTT was 15.6 months. Among these patients, the average age was 46 years

Table 1 Patient and tumor characteristics

	Total	Plat/Etop	Mit	Mit/Plat/Etop	Mit/Other	Plat/Etop/Other	Misc cyto
Number of patients	57	16	12	11	5	3	10
Age at diagnosis (years)	44.6 ± 3.8	46.5 ± 7.9	41.4 ± 7.7	43.4 ± 6.4	33.2 ± 14.7	65 ± 5.2	44.6 ± 8.4
Sex							
F	37	11	7	5	3	2	9
M	20	5	5	6	2	1	1
Primary size (cm)	12.1 ± 1.4	10.4 ± 1.9	16.25 ± 4.1	10.5 ± 2.0	8.9 ± 3.5	12.5 ± 2.5	14.6 ± 3.1
Local disease[a] (%)	24 (42.1)	9 (56)	3 (25)	5 (45.5)	3 (60)	1 (33)	3 (30)
Lung metastases (%)	31 (54.4)	7 (44)	6 (50)	6 (54.5)	4 (80)	1 (33)	7 (70)
Liver metastases (%)	27 (47.4)	9 (56)	5 (41.7)	4 (36.4)	1 (20)	2 (66)	6 (60)
Bone metastases (%)	6 (10.5)	3 (19)	0	1 (9.1)	1 (20)	0	1 (10)
Peritoneal metastases (%)	15 (26.3)	1 (6)	5 (41.7)	3 (27.3)	2 (40)	1 (33)	3 (30)
Cushing's syndrome (%)	23 (40.4)	8 (50)	3 (25)	4 (36.4)	4 (80)	1 (33)	3 (30)

Etop, etoposide; F, female; M, male; Misc Cyto, miscellaneous cytotoxics; Mit, mitotane; Plat, platinum.
[a]Primary adrenal tumor or adrenal bed recurrence.

(range, 19–73 years), 14 had stage IV disease at the time of chemotherapy, and two had stage III ACC. Of the 16 patients, seven had a history of previous surgery before chemotherapy, of whom one patient had concurrent metastatic disease at the time of operation; the mean time from initial surgery to chemotherapy in this group was 19 months. The remaining nine of the 16 patients who received platinum/etoposide chemotherapy had had no prior surgery. Among all 16 patients at the time of chemotherapy, 10 (62%) had local disease in the adrenal gland/adrenal bed, nine (56%) had liver metastases, seven (44%) had lung metastases, three (19%) had bone metastases, and one (6%) had peritoneal involvement. Among the 16 patients, the median OS was 9.6 months and the median TTP was 4 months (Table 2). At the last follow-up, one patient was still alive 201 months from the date of first treatment; this statistic was censored from the OS analysis.

Mitotane

Twelve patients received mitotane alone as first-line systemic therapy for ACC, the mean TTT was 24.9 months. The average age of these patients was 41 years (range, 17–63) and all of them had stage IV disease when they received mitotane. Eleven patients had had surgery before receiving mitotane, four of whom had metastatic disease diagnosed at the time of surgery. The mean time from the original surgery to the start of mitotane in these 11 patients was 25 months, and in the four patients with metastases at the time of surgery, it was 1.75 months. One patient did not have prior surgery before starting mitotane therapy. At the initiation of mitotane, three (25%) of 12 patients had local disease in the adrenal gland/adrenal bed, six patients (50%) had lung metastases, five (42%) had liver metastases, five (42%) had peritoneal metastases, and none had bone involvement. Mitotane levels were documented in five patients and reached the target range of 14–20 mg/l in four of the five patients. The median OS was 23.3 months and the median TTP was 6.2 months (Table 2). At last follow-up four patients were still alive, their statistics were censored from OS analysis. The durations from first systemic treatment to last follow-up were 15, 31, 31, and 65 months in these four patients.

Table 2 Kaplan–Meier estimates of overall survival and time to progression with miscellaneous cytotoxics, mitotane, mitotane/platinum/etoposide, and platinum/etoposide

	N	Events	Median (months)	Lower 95% confidence limit	Upper 95% confidence limit
Overall survival		Deaths			
Misc cytotoxics	10	10	24.92	9.30	29.08
Mitotane only	12	8	23.33	12.75	79.38
Mitotane/Plat/Etop	11	8	22.97	7.56	93.14
Plat/Etop	16	15	9.6	7.06	25.27
Time to progression		Progress			
Misc cytotoxics	10	10	2.00	1.35	3.32
Mitotane only	12	11	6.24	3.58	32.13
Mitotane/Plat/Etop	11	11	4.01	3.68	14.20
Plat/Etop	16	15	4.01	2.96	7.29

Etop, etoposide; Misc, miscellaneous; Plat, platinum.

Mitotane, platinum, and etoposide

Eleven patients in our study were treated with a combination of mitotane, platinum, and etoposide; the mean TTT was 16.9 months. The mean age of these patients was 43 years (range, 19–69 years) and all 11 had stage IV disease at the time of chemotherapy. Eight of the 11 patients had a history of surgery before receiving systemic treatment, and three of the eight patients had diagnosed metastases at the time of surgery. The mean durations from initial surgery to chemotherapy were 21 months in the eight patients and 0.9 months in the three patients with metastases at the time of surgery. The remaining three of the 11 patients had metastatic disease and proceeded to chemotherapy without surgery. At the time of chemotherapy, six patients (55%) had lung metastases, six (55%) had local disease in the adrenal gland/adrenal bed, four (36%) had liver metastases, three (27%) had peritoneal metastases, and one patient (9%) had bone metastases. Mitotane levels were documented in only two patients, and in both cases were within therapeutic range. The median OS for all 11 patients was 23 months and the median TTP was 4 months (Table 2). At the last follow-up, three patients were still alive and their statistics were censored from the OS analysis. The durations from first systemic treatment to last follow-up in these three patients were 25, 28, and 47 months.

Mitotane and other agents

Five patients were treated with mitotane and other cytotoxic agents that did not include combination platinum and etoposide, the mean TTT was 16 months. In this group, two patients received mitotane and gemcitabine, one received mitotane with cisplatin, one received mitotane, carboplatin, and paclitaxel (Taxol), and one patient received mitotane, etoposide, adriamycin, and vincristine. The two patients treated with mitotane and gemcitabine were males aged 17 and 34 years. The younger of those patients was diagnosed with a recurrence of ACC involving the adrenal bed, peritoneum, and bone 7 months after an initial surgery for localized disease; after the initiation of chemotherapy, he achieved a maximum mitotane level of 9.5 mg/l. His OS and TTP were 18.3 and 2.3 months, respectively. The older patient had lung metastases at presentation and proceeded directly (without surgery) to chemotherapy, his OS and TTP were 29.9 and 2.5 months, respectively. One patient (female, age 17) was treated with mitotane and platinum at presentation for metastatic ACC to the lungs and liver; mitotane levels for her were not available, but her OS and TTP were 27.3 and 7.1 months, respectively. Another patient (female, age 53) received mitotane, platinum, and paclitaxel for recurrence of cancer in the adrenal bed, peritoneum, and lungs after

previous surgery for localized disease; her OS and TTP were 18 and 3.4 months, respectively. One patient (female, age 46) received mitotane, etoposide, doxorubicin, and vincristine for recurrence of ACC in the adrenal bed and lungs 36 months after her initial surgery; her OS and TTP were 46.7 and 2.2 months, respectively.

Platinum, etoposide, and other agents

Three patients received combination platinum and etoposide with other cytotoxic agents, the mean TTT was 32.5 months. One patient (male, age 69) received cisplatin, etoposide, and adriamycin for ACC with liver and lung metastases at presentation, OS and TTP were 7.1 and 4.9 months, respectively. One patient (female, age 60) was treated with cisplatin, etoposide, doxorubicin, and mitotane for recurrence of ACC in the liver. This patient was alive at last follow-up, 26.5 months after her first systemic treatment, and her statistics were censored from the OS analysis (TTP was 3.8 months). One patient (female, 66 years) received cisplatin, etoposide, and ifosfamide after a peritoneal recurrence of ACC 20 months after surgery for localized disease; her OS and TTP were 57.3 and 29.2 months, respectively.

Miscellaneous agents

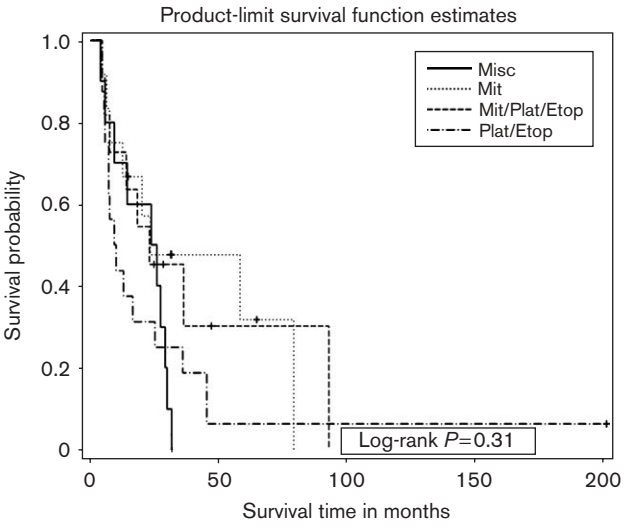
Ten patients were treated with various single agents or combinations: three patients received gemcitabine; three received paclitaxel; two were treated with cisplatin, adriamycin, and cyclophosphamide; one received cisplatin, adriamycin, and ifosphamide; and one patient was treated with adriamycin; the mean TTT for the entire group was 24.8 months. The three patients who received gemcitabine (38, 52, and 55 years of age) had stage IV disease at the time of treatment: all three had lung metastases, two had adrenal gland/adrenal bed tumors, one had liver involvement, and one had bone metastases. The OSs for these patients were 23.8, 31.9, and 26.1 months; their TTPs were 3.3, 10.5, and 1.3 months. Of the three patients who received paclitaxel (age 40, 59, and 68 years), all had liver metastases and two had lung nodules. The OSs for these patients were 9.3, 29.8, and 14.4 months, and their TTPs were 1.3, 1.4, and 2.4 months. Two patients (age 22 and 37 years) received cisplatin, adriamycin, and cyclophosphamide for recurrence of ACC in the liver (both patients) and lungs (younger patient) after surgery; OS and TTP were 4 and 1.5 months, respectively, in the younger patient, and 29.1 and 2.1 months, respectively, in the older patient. In one patient (age 38 years) who received cisplatin, adriamycin, and ifosfamide for metastatic disease (lungs and peritoneum) at presentation, OS and TTP were 27.2 and 8.8 months, respectively. One patient (age 37 years) was treated with single-agent adriamycin for peritoneal metastases; his OS and TTP were 5.8 and 1.9 months, respectively.

Log-rank and Cox regression analysis

Kaplan–Meier estimates of median OS and TTP for mitotane, mitotane/platinum/etoposide, platinum/etoposide, and miscellaneous cytotoxic agents are shown in Table 2. We included the last group because it was comparable in size to the other groups and would function as standard of comparison with the other groups (i.e. were any of the treatment groups superior to a random collection of agents and combinations).

The OS was 24.9 months in the miscellaneous cytotoxic group, 23.3 months in the mitotane group, 23 months in the mitotane/platinum/etoposide group, and 9.6 months in the platinum/etoposide group. Kaplan–Meier curves for OS are shown in Fig. 1. Log-rank testing did not identify any statistically significant difference in OS among the four groups ($P = 0.31$). A Cox regression model was used to identify variables contributing to OS (Table 3). On univariate analysis, patient age ($P = 0.90$), sex ($P = 1.0$), and presence of Cushing's syndrome ($P = 0.10$) were not found to have any significant effect on OS. Peritoneal metastasis had statistical significance on both univariate ($P = 0.02$) and multivariate ($P = 0.04$) analysis, and was the only variable associated with a 'protective' hazard ratio (HR) of 0.49 [95% confidence interval (CI), 0.24–0.98]. Metastatic disease to the liver had statistical significance on univariate ($P = 0.03$) but not multivariate ($P = 0.05$) analysis. Local disease ($P = 0.09$), metastatic disease in the lungs ($P = 0.82$), and metastatic disease in the bones ($P = 0.80$) did not have statistical significance. No statistical significance

Fig. 1



Kaplan–Meier curve of overall survivals with mitotane only, mitotane/platinum/etoposide, platinum/etoposide, and miscellaneous cytotoxics. Log-rank=0.13; Etop, etoposide; Misc, miscellaneous; Mit, mitotane; Plat, platinum.

Table 3 Univariate and multivariate model for overall survival

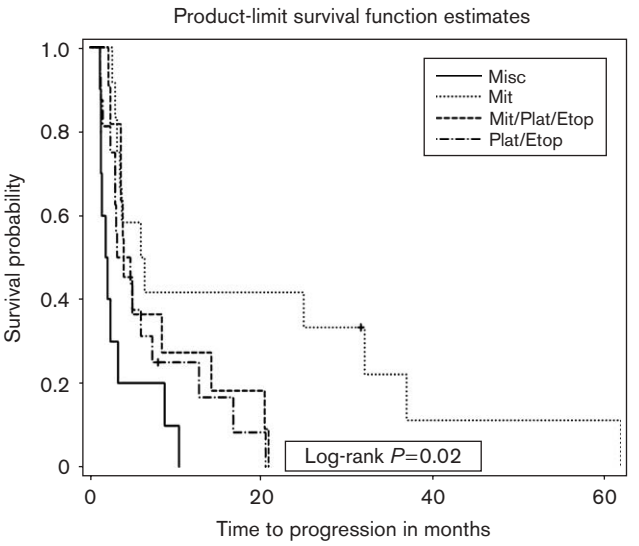
	Univariate model				Multivariate model			
Parameter	*P* value	Hazard ratio	95% CI lower	95% CI upper	*P* value	Hazard ratio	95% CI lower	95% CI upper
Age	0.90	1.00	0.98	1.02				
Sex								
M (ref: F)	1.00	1.00	0.55	1.82				
Chemo[a]								
Misc	0.11	2.18	0.83	5.70				
M/P/E	0.73	1.19	0.44	3.21				
M/other	0.29	1.94	0.57	6.61				
P/E	0.12	2.01	0.84	4.80				
P/E/other	0.99	1.01	0.21	4.78				
Cushing's syndrome								
Y (ref: n)	0.10	1.67	0.90	3.09				
Local lesions								
Y (ref: n)	0.09	1.65	0.93	2.95				
Liver mets								
Y (ref: n)	**0.04**	1.84	1.05	3.24	0.05	1.86	1.01	3.42
Lung mets								
Y (ref: n)	0.82	1.07	0.61	1.85				
Bone mets								
Y (ref: n)	0.80	0.90	0.38	2.12				
Peritoneal mets								
Y (ref: n)	**0.02**	0.46	0.24	0.86	**0.04**	0.49	0.24	0.98

Local lesions include both primary adrenal tumors and adrenal bed recurrences.
CI, confidence interval; E, etoposide; F, female; M, male; M, mitotane; Mets, metastases at the time of medical therapy; Misc, miscellaneous cytotoxics; Other, other cytotoxics; P, platinum; ref: n, reference no; Y, yes.
[a]Reference mitotane only.
Bold indicates statistical significance ($P<0.05$).

on univariate analysis of the six treatment groups was observed.

The TTP was 6.2 months in the mitotane-treated group, 4 months in the mitotane/platinum/etoposide group, 4 months in the platinum/etoposide group, and 2 months in the miscellaneous cytotoxic group. A Kaplan–Meier plot of TTP is shown in Fig. 2. Log-rank testing indicated a statistically significant difference ($P = 0.02$) in TTP among the groups, favoring single-agent mitotane. This difference was maintained when mitotane was compared with platinum/etoposide ($P = 0.04$) but was not when mitotane was compared with mitotane/platinum/etoposide ($P = 0.47$). Using the Cox regression model (Table 4), patient age ($P = 0.65$), sex ($P = 0.49$), and presence of Cushing's syndrome ($P = 0.56$) were not significant on univariate analysis of TTP. Peritoneal metastasis was significant for increased TTP on both univariate ($P = 0.01$) and multivariate analyses ($P < 0.01$), with a HR of 0.31 (95% CI, 0.14–0.69) (Table 4). Liver metastasis was significant for TTP on univariate analysis ($P = 0.03$) but not on multivariate analysis ($P = 0.19$). Local disease ($P = 0.65$) and disease in the liver ($P = 0.18$), lungs ($P = 0.21$), and bone ($P = 0.93$) did not have any significant influence on TTP. The miscellaneous cytotoxic group had a statistically significant decreased TTP on both univariate ($P < 0.01$) and multivariate analyses ($P < 0.01$), with a HR of 8.23 (95% CI, 2.90–23.39). The mitotane with other cytotoxic group also had a decreased TTP on univariate ($P = 0.02$) and multivariate analyses ($P = 0.03$), with a HR of 4.08 (95% CI, 1.12–14.86) (Table 4).

Fig. 2



Kaplan–Meier curve of time to progression with mitotane only, mitotane/platinum/etoposide, platinum/etoposide, and miscellaneous cytotoxics. Log-rank = 0.02; Etop, etoposide; Misc, miscellaneous; Mit, mitotane; Plat, platinum.

Discussion

The objective of our study was to describe our institution's experience over the last two decades with various first-line chemotherapies for ACC to contribute to and perhaps further elucidate the cumulative body of information on this rare cancer and its treatment. In our

Table 4 Univariate and multivariate models for time to progression

	Univariate model				Multivariate model			
Parameter	*P* value	Hazard ratio	95% CI lower	95% CI upper	*P* value	Hazard ratio	95% CI lower	95% CI upper
Age	0.65	1.00	0.98	1.02				
Sex								
M (ref: F)	0.49	0.81	0.45	1.47				
Chemo[a]								
Misc	**<0.01**	6.76	2.40	19.02	**<0.01**	8.23	2.90	23.39
M/P/E	0.06	2.57	0.96	6.84	0.23	1.83	0.68	4.92
M/other	**0.01**	5.96	1.64	21.73	**0.03**	4.08	1.12	14.86
P/E	**0.02**	3.18	1.24	8.20	0.15	2.03	0.77	5.31
P/E/other	0.93	1.07	0.23	5.05	0.88	1.13	0.24	5.37
Cushing's syndrome								
Y (ref: n)	0.56	1.19	0.67	2.12				
Local lesions								
Y (ref: n)	0.65	1.14	0.65	1.99				
Liver metastases								
Y (ref: n)	0.18	1.46	0.84	2.56				
Lung metastases								
Y (ref: n)	0.21	1.46	0.81	2.64				
Bone metastases								
Y (ref: n)	0.93	1.04	0.44	2.46				
Peritoneal metastases								
Y (ref: n)	**0.01**	0.36	0.18	0.75	**<0.01**	0.31	0.14	0.69

Local lesions include both primary adrenal tumors and adrenal bed recurrences.
CI, confidence interval; E, etoposide; F, female; M, male; M, mitotane; metastases are those at the time of medical therapy; Misc, miscellaneous cytotoxics; Other, other cytotoxics; P, platinum; ref: n, reference no; Y, yes.
[a]Reference mitotane only.
Bold indicates statistical significance ($P<0.05$).

analysis, we found no clear advantage in OS between patients in any of the various treatment groups studied. OS following mitotane, platinum, and etoposide was not significantly different from OS after platinum and etoposide without mitotane, and neither combination was superior to single-agent mitotane. The Cox regression model suggested a worse outcome in TTP, but not OS, in the miscellaneous cytotoxic and the mitotane with other cytotoxic treatment groups. However, the heterogeneity of our treatment groups and the low number of patients treated with certain agents and combinations made direct comparisons challenging.

Over the last 20 years, the range of chemotherapeutic options for ACC has not broadened significantly despite reportedly poor outcomes for patients with advanced disease. The systemic agents for ACC most commonly described in the literature have been mitotane, etoposide, and cisplatin, used together or in various combinations with other agents. Overall response rates have typically varied from 11 to 30% [9–12]. In a phase II trial, Berruti *et al.* [13] prospectively assigned 75 patients to treatment with cisplatin, etoposide, doxorubicin, and mitotane. Of the 75 patients, five achieved a complete response and 30 had a partial response, for an overall response rate of 48.6%. The experience of Berruti *et al.* is the most successful response to systemic therapy for ACC reported to date. In our cohort, the one patient who received cisplatin, etoposide, doxorubicin, and mitotane during the study period was noted to have an OS of 100 months but was censored from the analysis of OS. Publication of the findings by Berruti *et al.* corresponded with the end date of our study period, which explains why there were not more patients treated with this combination in our series.

Mitotane, an adrenolytic derivative of the insecticide dichloro-diphenyl-trichloroethane has been used with variable success for over 45 years in the treatment of ACC. We previously published findings for a series of 72 ACC patients treated at our institution with single-agent mitotane, some of whom are included in our current analysis; 21 patients achieved a partial response and no complete responses were observed, for an overall response rate of 29% [14]. Other published reports have described similar response rates to single-agent mitotane [15–19]. In our current study, we observed that patients treated with single-agent mitotane had a statistically significant advantage in TTP compared with patients in the other treatment groups. The dose of mitotane used for our patients ranged from 1.5 to 15 g per day, with the majority of patients receiving between 2 and 4 g per day. Measurement of a patient's mitotane levels only became possible in the early 1990s; patients treated before that typically had their mitotane dose titrated to their symptoms. In the patients who did have plasma levels of mitotane measured, most were within the accepted therapeutic range of 14–20 mg/l.

The decision to treat advanced ACC with single-agent mitotane over systemic chemotherapy is based upon the overall tumor burden at the time of treatment and the rate of growth of the lesions. Out of convention, a patient with metastatic ACC that demonstrates a rapid

pattern of tumor growth will more often be prescribed systemic chemotherapy over single-agent mitotane therapy. This seems to be owing to a perception that chemotherapy offers a more aggressive approach to treatment than mitotane alone. In our study, all patients who received single-agent mitotane therapy had metastatic disease at the time of treatment. However, we could not consistently calculate the rate of tumor growth preceding the decision to place patients on single-agent mitotane, so it is uncertain whether the pattern of practice favored treating patients with more slowly growing metastatic lesions with single-agent mitotane. Therefore, we are unable to conclude whether any disparity in the rate of cancer growth in the single-agent mitotane group, compared with the other treatment groups, may have contributed to the favorable findings in TTP single-agent mitotane group.

Patients with localized ACC (stages I and II) have been shown to have significantly better 5-year survival rates than patients with advanced ACC (stages III and IV) have (3,6), suggesting that a determinant of OS might be the total tumor burden, particularly the presence of metastases. A recent study by Assie *et al.* [20] investigated prognostic parameters in metastatic ACC. In these investigators' review of 124 patients with metastatic ACC, univariate analysis suggested that liver and bone metastases and greater numbers of metastatic lesions, tumor-involved organs, and mitoses all had an adverse effect on survival. However, only greater numbers of tumor-involved organs ($P = 0.0058$) and mitoses ($P = 0.049$) were statistically significant on multivariate analysis. In our series, all patients had advanced disease at the time of systemic therapy; the distribution and frequency of organ metastases in our patients were similar to those in other published reports [15]. We evaluated the number of tumor-involved organs in our patients, using the cutoff of three organs as a negative prognostic marker, as described by Assie *et al.* [20]. In our series, we were unable to show a statistically significant difference in OS between patients with three tumor-affected organs and those with one or two affected organs ($P = 0.4$; data not shown). In our univariate analysis, lung, and bone metastases did not have a significant effect on OS. Liver metastasis was associated with a shorter OS on the univariate analysis but was not statistically significant on the multivariate analysis. Variables such as patient age, sex, and the presence of hypercortisolemia did not have a statistically significant effect on survival outcome in our patients.

An interesting observation that emerged in both the univariate and multivariate analyses in our current study was the longer OS and TTP associated with peritoneal metastases than that with metastases at other sites. Fifteen patients in our series had peritoneal metastases; their median OS was 28.6 months and their median TTP was 5.6 months. Of the 15 patients, three had disease limited to the peritoneum, six had one additional metastatic organ site, and six had two additional metastatic organ sites. Eight of the 15 patients had disease either limited to the peritoneum or also in the adrenal gland/adrenal bed. As metastatic implants in the peritoneum and adrenal bed are likely the result of tumor seeding owing to disruption of the original tumor capsule, it is likely that the biology of the seeded cells in this location is different from that of cells elsewhere that have acquired the capability for hematogenous spread and invasion of distant sites such as the lungs, liver, and bones. The favorable effect associated with peritoneal metastases did not, however, represent a protective phenomenon. Rather, patients in our study who did not have peritoneal metastases had other sites of metastatic disease. Therefore, the beneficial effect associated with peritoneal metastases is relative to the outcome in patients with distant metastases at other sites. This may suggest that peritoneal metastases respond better to systemic chemotherapy than do metastases at other distant sites. However, determining the prognostic effect of different metastatic sites was not the primary objective of our study and the number of patients included within our retrospective series does not necessarily ensure the appropriate power to draw these conclusions.

Our study has several strengths. First, it is a single-institution experience encompassing a significant number of patients with a very rare disease. Moreover, whereas most published experiences to date have described outcomes associated with a single agent or drug combination, our study also directly compared different chemotherapies within a single patient cohort. Additionally, most of the patients in our study were treated by one of the authors, ensuring a level of consistency in the medical record.

Our study was a retrospective review and was therefore subject to the limitations inherent in the study design. Only patients with comprehensive medical records and extensive follow-up were included, and this may have resulted in selection bias. Likewise, the possibility of selection bias must be considered where patients were assigned to receive systemic cytotoxic therapy versus single-agent mitotane, as physicians will typically prescribe the former for rapidly growing, aggressive disease. Although patients treated with systemic cytotoxic agents in our study received standard doses of each agent, consistent with conventional practice, there was the potential for treatment bias as there may have been some variation in doses of agents among treatment groups.

Conclusion

In our analysis, we found no clear survival advantage for any single agent or combination over any of the other conventional first-line chemotherapeutic choices for ACC. Mitotane may delay TTP but was not associated

with longer survival times than were other agents or combinations studied. The evidence for first-line therapy remains limited, and current consensus guidelines continue to favor the use of mitotane, platinum, and etoposide in various combinations, largely because there are no satisfying alternatives [21]. To date, the combination of mitotane, etoposide, cisplatin, and doxorubicin has produced the highest reported response rate in patients with advanced ACC. An international collaboration of investigators has designed a prospective study (First International Randomized Trial for Locally Advanced and Metastatic Adrenocortical Tumors) to directly compare this drug combination with streptozotocin and mitotane, as the latter has recently been described to offer benefit in the adjuvant setting against ACC [22]. Recent renewed interest in the use of adjuvant mitotane has also developed since the recent publication by Terzolo *et al.* [23] describing prolonged recurrence free survival in patients with radically resected ACC treated with mitotane.

Despite the general inertia in developing new drugs for the treatment for ACC over the last 20 years, prospective therapies are expected to emerge in the very near future. The recent proliferation of small-molecule inhibitors of protein kinases, particularly tyrosine kinases, may offer new targeted therapies for the treatment of ACC. Inhibitors of the vascular endothelial growth factor receptor, epidermal growth factor receptor, and insulin-like growth factor-1 receptor have tremendous theoretical potential, as they may be able to interrupt the key signaling pathways leading to tumorigenesis in this disease; several of these agents are under investigation and are currently in trials [24]. The outcome in advanced metastatic ACC with the current conventional first-line therapies remains poor, and novel agents are sorely needed for this aggressive cancer. The aforementioned recent advances bring the promise of new avenues of treatment for patients with advanced ACC, and with these new treatments will come the hope for improved outcome in this disease.

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