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Efficiency of platinum-based chemotherapy re-induction for adrenocortical cancer treatment.

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Abstract

The combination of platinum-based chemotherapy with mitotane (m) is the standard first-line therapy for metastatic adrenocortical cancer (ACC) with long-term disease control in approximately 25% of patients. Considering the lack of effective regimens for second and subsequent lines of therapy, it seems relevant to evaluate the effectiveness of platinum-based chemotherapy re-induction for patients with long platinum-free interval. Aim:Evaluation of the platinum-based chemotherapy re-induction efficiency with or without mitotane for patients with metastatic ACC.Materials and methods:This retrospective clinical study included patients with disease progression ≥ 6 months after completion of platinum-based chemotherapy for metastatic ACC. Results:17 patients were included, of which 16 received EDP+/-m regimen and 1 - EP. The median platinum-free interval was 8.3 months (7.2-39.7). Concurrent mitotane therapy was administered in 14 patients (82.35%), all of them achieved therapeutic concentration. Objective response and disease control ≥6 months rate were

observed in 23.52% (N=4) and 52.94% (N=9), respectively. The median progression-free survival was 6.17 months, and the median overall survival 15.63 months.Conclusion:This study demonstrated the efficacy of platinum-based chemotherapy re-induction in metastatic ACC. The selected group of patients in our study with relatively platinum-sensitive disease does not allow to perform cross trial comparisons. Based on the results described above, we recommend considering re-induction of platinum-based chemotherapy with mitotane for patients with a platinum-free interval of ≥6 months as an option of second or further lines of treatment.

Keywords: adrenocortical cancer, re-induction, platinum-based chemotherapy, EDP, mitotane.

Introduction

Adrenocortical carcinoma (ACC) is an orphan disease with poor prognosis. The Incidence of ACC in the United States is 2 cases per 1 million population per year (1).

Radical surgical treatment is the standard of care for local stages of ACC. However, the 5 years recurrence rate after surgical treatment ranges from 20% for ESNAT stage I to 70% for stage III (2). Based on the results of phase III FIRM-AKT study, the combination of EDP chemotherapy regimen (Doxorubicin 40 mg/m2 on day 1, Etoposide 100 mg/m2 on days 2-4 and Cisplatin 40 mg/m2 on days 3-4 every 4 weeks) with mitotane (m) is considered the most effective systemic therapy for metastatic and locally advanced ACC with objective response rate 23.2%, median progression-free survival (PFS) 5 months and one-year progression-free survival 26.1% (3). Similar data were obtained in a phase II clinical study, which evaluated the efficacy of docetaxel and cisplatin combination (4). In this study, prescribing of platinum-based chemotherapy without mitotane resulted in a partial response rate of 21% and one-year PFS 21%.

There are still no effective options for second and subsequent lines of chemotherapy. The most studied and commonly prescribed second-line chemotherapy regimen is combination of gemcitabine with capecitabine/5-FU and mitotane. The objective response rate for this regimen ranges from 4 to 7%, and the median PFS is 12 weeks (5,6).

The evaluation of the effectiveness of platinum-based chemotherapy re-induction seems to be relevant, considering the modest benefit of standard second- and subsequent-lines and high

sensitivity to platinum in 20-25% of patients with ACC (3,4). Any data on platinum-based chemotherapy re-induction have not been published yet.

The aim of this retrospective clinical study was to evaluate the effectiveness of platinum-based chemotherapy re-induction +/- mitotane in patients with metastatic ACC.

Materials and methods

Inclusion criteria

This retrospective clinical study included adult patients (older than 18 years) with histologically confirmed ACC who had disease progression no earlier than 6 months after the completion of platinum-based chemotherapy for metastatic disease with ECOG status 0-2.

Treatment schedule

Patients received EDP±m chemotherapy (Doxorubicin 40 milligrams/square meter (mg/m2) on cycle day 1, Etoposide 100 mg/m2 on cycle days 2-4, Cisplatin 40 mg/m2 on cycle days 3-4, every 4 weeks) or EP±m (Etoposide 100 mg/m2 on days 1-3 + Cisplatin 75 mg/m2 on day 1, every 3 weeks). The treatment plan was 6 cycles, than the patients continued mitotane as a maintenance therapy. Doxorubicin was continued until a cumulative dose of 450 mg/m2 was reached, after that chemotherapy was performed according to the EP scheme.

Safety monitoring

The concentration of mitotane, free T3 and T4, TSH, biochemical blood test (sodium, potassium, chlorine, alanine aminotransferase, aspartate aminotransferase) was assessed every 4 weeks of mitotane therapy. In cases of central neurological toxicity, with the concentration of mitotane above >20 μg/ml, mitotane was interrupted until the concentration decreased below <20 μg/ml, after that mitotane was resumed with a dose reduction by 1 g/day.

Electrocardiography and echocardiography were performed at baseline and every 3 cycles of chemotherapy. The left ventricular ejection fraction lower than 50% was a contraindication to doxorubicin administration.

Adverse events were assessed according to the General Terminological Criteria for Adverse Events, version 4.03.

Before each cycle of chemotherapy all patients must have had adequate clinical (neutrophils ≥1.5 * 10^9, platelets ≥100 * 10^9) and biochemical blood tests (liver enzymes <2.5 upper

limit of normal [ULN] or <5 ULN in the presence of metastases in liver, total bilirubin <1.5 ULN, glomerular filtration rate of at least 60 ml / min / 1.73 m2 according to CKD-EPI).

Tumor assessment

Therapy effectiveness was evaluated according to RECIST 1.1 criteria by chest, abdomen, and pelvis CT scans every 6-8 weeks .

Objective response rate, disease control rate, median PFS, median overall survival were assessed.

Statistical analysis

The platinum-free interval was defined as the time from completion of platinum-based chemotherapy to disease progression. Progression-free survival was assessed as the interval from initiation of therapy to disease progression based on radiological examination or death if no follow-up examination was performed. Overall survival was defined as the interval from the start of therapy to the date of death or last contact with the patient. The Kaplan-Meier method was used to estimate PFS and OS. Statistical calculations were performed with IBM SPSS Statistics Professional 20.0.

Results

17 patients were included in the study from March 2015 to May 2022, of which 16 received EDP+/-m chemotherapy and 1 EP+m regimen due to doxorubicin limit dose reaching in previous treatment lines. Median age was 45.47 years (range 31-62) at study entry, male/female ratio 53/47%, ECOG status assessed as 0-1 in 16 (94.12%) cases. The ki67 expression was evaluated in the primary tumor in 15 (88.24%) cases and in metastases' core-biopsy material in 2 (11.76%) and was found to be > 20% in 6 (35.29%).

All patients had disease progression in at least 6 months after completion of platinum-based chemotherapy for metastatic ACC. 16 patients had received EDP+/-m and one patient CAP regimen (doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 and cisplatin 50 mg/m2 every 3 week) in previous treatment lines. The median platinum-free interval was 8.3 months. (7.2-39.7 months), only 4 patients had platinum-free interval at least 1 year. In 14 patients (82.35%) re-induction of platinum-containing therapy was carried out as a second treatment line, in 3 (17.65%) as a third line. Demographic and baseline clinical characteristics are presented in Table 1.

Table 1. Demographic and baseline clinical characteristics of patients.

	N=17	%
Gender		
Male	9	52,94
Female	8	47,06
Age		
Mean, years	45,47 (31-62)	
Median, years	44	
ECOG		
0	6	35,29
1	10	58,82
2	1	5,88
Ki67		
0-10%	4	23,53
11-20%	5	29,41
>20%	6	35,29
No data	2	11,76
Location of metastases[1]		
Lung	15	88,24
Liver	14	82,35
Local recurrence	8	47,06
Bones	6	35,29
Number of prior systemic therapies		
1	14	82,35
2	3	17,65
Previous treatment lines		
EDP+/-m	16	94,12
CAP	1	5,88
GemCap+/-m	2	11,76

Concurrent mitotane		
Yes	14	82,35
No	3	17,65
Concentration of mitotane above 14 ng/ml		
Yes	14	82,35
Achieve in previous lines	12	70,59
Achieve in platinum-based therapy re-induction	2	11,76
Best response on the previous platinum-based therapy		
Partial response	6	35,29
Stable disease	11	64,71
Platinum-free interval		
≤12 months	13	76,47
>12 months	4	23,53
Median, months	8,30 (7.2-39.7)	
Mean, months	10,50	

1- Can be more than one metastasis location.

Concurrent mitotane therapy was administered in 14 patients (82.35%), all of them reached therapeutic concentration, mostly (70.59%) in previous treatment lines. In 3 cases mitotane was not prescribed due to lack of access to the drug.

Efficacy

Treatment plan (6 cycles of therapy) was completed in 9 patients (52.94%). Disease progression was observed in 13 patients (76.4%) with a median of follow-up 12.93 months.

There were no complete responses. Partial response was registered in 4 (23.52%) cases, stable disease in 7 (41.18%). Disease control rate for at least 6 months was 54.92% (N=9). The best overall responses according to RECIST 1.1 are presented in Table 2.

Table 2. The best overall response according to RECIST 1.1

	N=17	%
Complete response	0	0,00
Partial response	4	23,53
Stable disease	7	41,18
Disease control at least 6 months	9	52,94
Progressive disease	6	35,29

Median PFS was 6.17 months. (95% CI 0.79-11.54) [figure 1]. The median duration of disease control (objective response + stable disease) was 11.37 months (figure 2), in 4 patients (23.52%) it lasted for more than 2 years . The median overall survival was 15.63 months (95% CI 4.95-39.32) [figure 3].

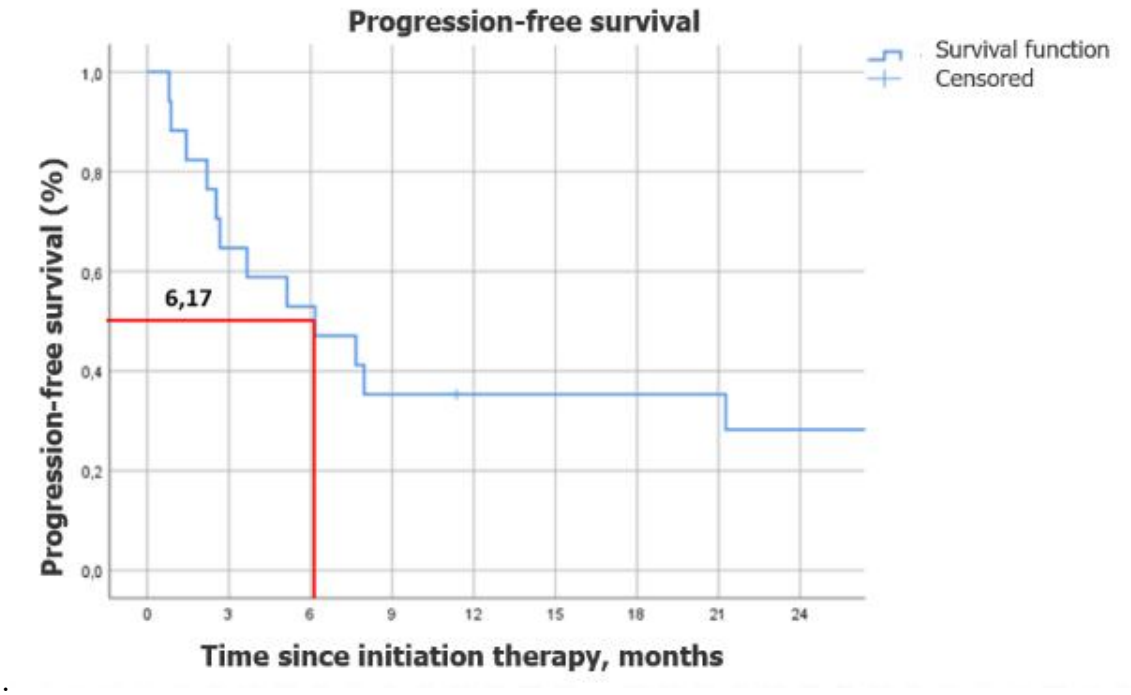

Figure 1. Progression-free survival.

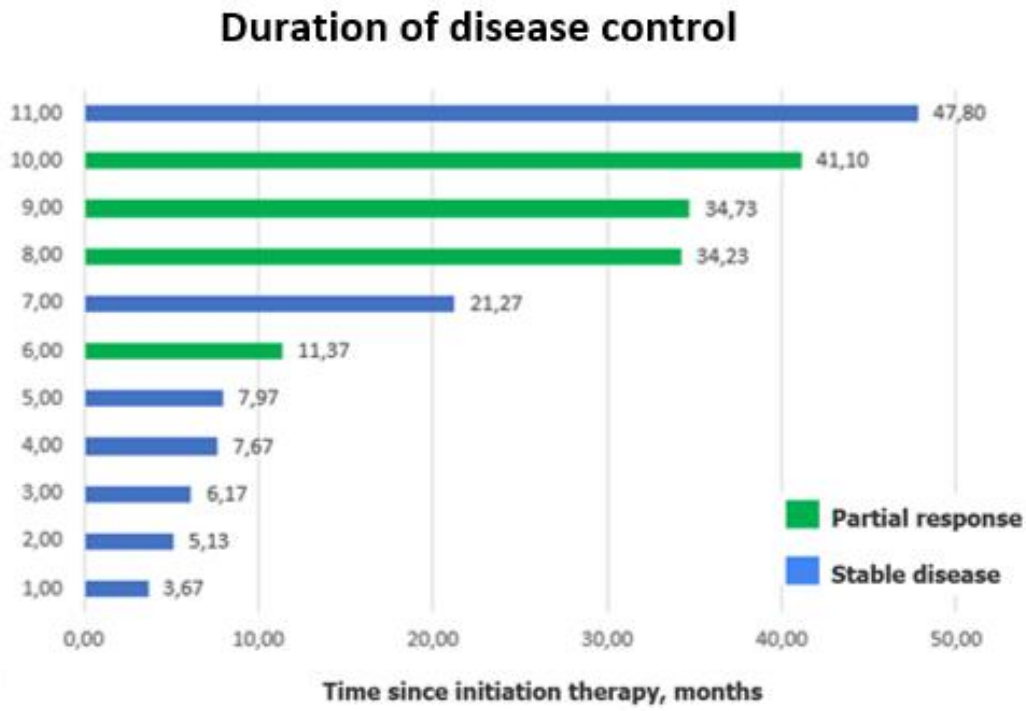

Figure 2. Duration of disease control.

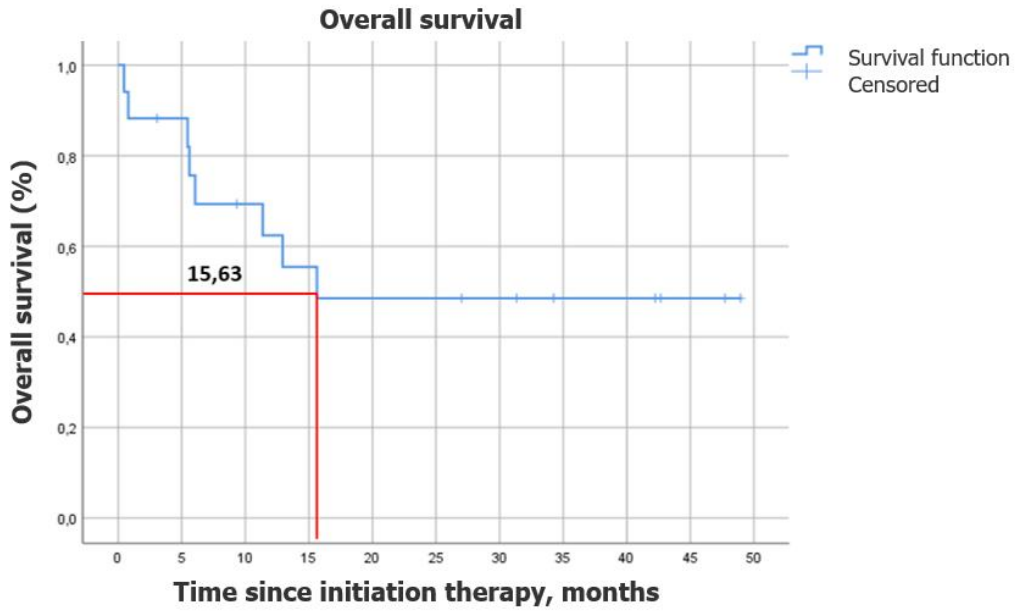

Figure 3. Overall survival.

Discussion

This is the first study to demonstrate the efficacy of platinum-based chemotherapy re-induction ± mitotane for metastatic ACC in subgroup with platinum-free interval for at least 6 months. The objective response rate and the PFS observed is similar to the data shown in the

FIRM-AKT study where EDP+m regimen was prescribed in the first treatment line (4). In our cohort of patients, the therapeutic concentration of mitotane was reached in previous treatment lines in more than 70% of cases, which determines the main role of the chemotherapeutic component of the regimen in disease control. The limitation of our study is a small number of patients and retrospective design. Moreover, in the majority of cases (65%) ki67 was defined as <20%, which is associated with relatively good prognosis (7, 8).

Adrenocortical cancer is an orphan disease and only 20-25% of patients who received platinum-containing chemotherapy could be candidates for re-induction of platinum drugs (platinum-free interval ≥6 months), which makes it difficult to compare the effectiveness of re-induction with the standard regimen of second and subsequent lines - GemCap+m in the prospective studies. The selected group of patients in our study with relatively platinum-sensitive disease does not allow to perform cross trial comparisons. In respect that in previous retrospective study no significant differences were observed between patients treated with GEM-based chemotherapy as first-/second-line treatment or in later lines (6) we recommend considering re-induction of platinum-based chemotherapy in combination with mitotane in subgroup of patients with platinum-free interval for at least 6 months as an option of second or further lines of treatment.

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