Original Article

Efficacy of cyclophosphamide, doxorubicin, and cisplatin for adenoid cystic carcinoma, and their relationship with the pre-chemotherapy tumor growth rate

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Background: While surgical resection is the treatment of choice for adenoid cystic carcinoma (ACC), patients with metastasis and those who cannot undergo surgery receive palliative chemotherapy. However, the role of palliative chemotherapy is not clear yet. This study aimed to evaluate the efficacy of chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) for patients with ACC; and to analyze the relationship between the pre-chemotherapy tumor growth rate (P-TGR) and treatment outcomes in patients with the recurred metastatic unresectable ACC.

Methods: We retrospectively analyzed the clinical data and treatment outcomes of patients who diagnosed ACC and treated with CAP chemotherapy. Response evaluation was performed using computed tomography (CT) images obtained before and after chemotherapy according to the RECIST 1.1. P-TGR was defined as the difference of the sum of the largest diameter of the target lesion per unit of time between the pre-baseline and baseline CT images.

Results: Fourteen patients with ACC who were treated with CAP were enrolled. Median patient age was 49 years, and the patients received a median of 5 CAP treatment cycles. Two patients achieved partial response (PR) and 10 patients showed stable disease. Response rate was 14.3%, and the disease control rate was 85.7 %. Median progression-free survival was 5.7 months (95% CI: 4.3 to not reached) and the median overall survival was 23.4 months (95% CI: 12.9 to not reached). A low P-TGR was associated with a good response to CAP (correlation coefficient, 0.56).

Conclusions: Palliative CAP chemotherapy demonstrated a modest anti-cancer effect for ACC. A low P-TGR was associated with a good response to CAP chemotherapy.

Keywords: Cyclophosphamide; doxorubicin; cisplatin; tumor growth rate; adenoid cystic carcinoma (ACC)

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Introduction

Adenoid cystic carcinoma (ACC) is a rare cancer that occurs mainly in the salivary gland. ACC accounts for approximately 10% of salivary neoplasms and 1% of head and neck cancer cases (1). The most common sites of ACC are the minor salivary gland and submaxillary sinus (2). ACC is an indolent tumor that grows slowly, but commonly metastasizes to the lungs and bones (3,4).

The standard treatment for ACC is surgical resection and/or radiotherapy according to the tumor site, stage,

and histologic grade (5,6). However, approximately 60% of patients who undergo resection eventually experience relapse with or without distant metastasis, and they have a poor prognosis (7). Chemotherapy is administered for advanced, relapsed, or metastatic ACC; however, ACC does not respond well to palliative chemotherapy (8). Although several phase II studies on palliative cytotoxic chemotherapy for ACC have been reported, the response rate is mostly <20% (8,9). Therefore, the role of palliative chemotherapy for ACC is still controversial because of its chemo-resistance and the lack of large-sized studies evaluating this issue.

Patients with metastatic ACC usually show an indolent asymptomatic clinical course without active treatment. However, metastatic lesions eventually grow rapidly and the patient becomes symptomatic, although many metastatic ACC lesions usually present as stable disease without active chemotherapy till a certain time point. Therefore, it is not easy for clinicians to decide when to initiate chemotherapy. Based on the results of several phase II studies, some experts prefer to administer chemotherapy when the tumor starts growing rapidly or when the patient starts showing symptoms. However, there are no data regarding the pre-chemotherapy growth velocity and the optimal timing for initiating chemotherapy. Furthermore, when physicians encounter a stable disease rate in phase II trials, it is difficult to distinguish between natural stable disease without chemotherapy and active disease control owing to chemotherapy (10).

Therefore, in this study, we evaluated (I) the efficacy of cyclophosphamide, doxorubicin, and cisplatin (CAP) combination chemotherapy, and (II) analyzed the relationship between the pre-chemotherapy tumor growth rate (P-TGR) and treatment outcomes of CAP.

Methods

Patient population

We retrospectively reviewed the medical records of patients diagnosed with ACC and treated with CAP chemotherapy at Seoul National University Hospital (SNUH) between November 2015 and December 2018. The diagnosis was confirmed pathologically.

We included patients aged 18 years or older, who had a measurable lesion according to the Response Evaluation Criteria for Solid Tumors (RECIST 1.1) (11), an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2, and adequate hematologic, hepatic, and renal functions.

Treatment schedule and calculation of the tumor growth rate

Patients were treated with palliative CAP, with 750 mg/m^2 cyclophosphamide, 60 mg/m^2 cisplatin, and 40 mg/m^2 doxorubicin, all administered intravenously on day 1 every 3 weeks. Chemotherapy was continued for a maximum of 6 cycles owing to the cumulative cardiac toxicity of doxorubicin. Response evaluation was performed according to the RECIST 1.1. P-TGR was defined as the difference in the sum of the largest diameter of the target lesion per unit of time between the pre-baseline and baseline CT images: $(S_0 - S_{pre})/(T_0 - T_{pre})$, where S_0 and S_{pre} indicate the sum of the largest diameter of target lesions at pre-baseline and baseline, while T_0 and T_{pre} indicate the pre-baseline and baseline time (12). Tumor shrinkage% was defined as the largest difference in the sum of the target lesion between baseline and after CAP chemotherapy.

Progression-free survival (PFS) was defined as the time between the first day of CAP to the date of disease progression or death. Overall survival (OS) was defined as the time between the first day of CAP to the date of death. Median PFS, OS, and follow-up period were calculated using the Kaplan-Meier method. The relationship between P-TGR and tumor shrinkage% after CAP was analyzed by using the Pearson method. Statistical analysis was performed using R version 3.5.3 (R Development Core Team, https://www.r-project.org/).

Ethical considerations

The study protocol was reviewed and approved by the Institutional Review Board of SNUH (approval number: H-1812-059-993). This study was conducted according to the guidelines for biomedical research and Declaration of Helsinki. The need for informed consent from patients was waived owing to the retrospective nature of the study.

Results

Patient characteristics

A total of 14 patients (6 men, 8 women) were enrolled in this study. The baseline characteristics of the patients are summarized in *Table 1*. The median patient age was 49 years

Table 1 Baseline characteristics

N=14	Number (%)
Sex	
Male	6 (42.9)
Female	8 (57.1)
Age	
Median (range)	49 (39–57)
Primary site	
Maxillary sinus	3 (21.4)
Sublingual gland	2 (14.3)
Submandibular gland	2 (14.3)
Palate	2 (14.3)
Gingiva	1 (7.1)
Tonsil	1 (7.1)
Lip	1 (7.1)
Parotid gland	1 (7.1)
Lacrimal gland	1 (7.1)
Initial stage at diagnosis	
I	2 (14.3)
II	2 (14.3)
III	2 (14.3)
IV	8 (57.1)

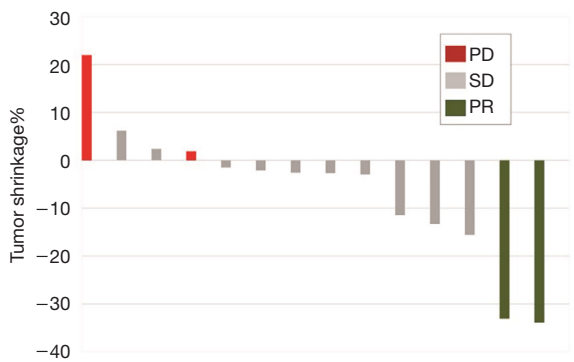

Figure 1 Waterfall graph for tumor shrinkage% after cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy.

(range, 39-57 years). The most common primary sites of ACC were the sublingual gland and the maxillary sinus in 3 patients. Eight patients were had stage IV ACC at the time of diagnosis. All patients included in this study received prior local treatment before CAP chemotherapy, except for 1 patient: 10 patients underwent surgical treatment and 13 patients received prior radiotherapy. Five patients received other systemic treatment including chemotherapy and tyrosine kinase inhibitors. The median time from initial diagnosis of ACC to CAP chemotherapy was 51.0 months (range, 1.8–268.6 months). The median follow-up duration was 29.2 months.

Treatment outcomes

The patients received a median of 5 cycles of CAP (range, 2–6 cycles). *Figure 1* shows the waterfall graph for the tumor shrinkage% after CAP chemotherapy. Two patients achieved partial response (PR) and 10 patients showed stable disease (71.4%). Overall response rate was 14.3% (95% CI, −4.0% to 32.6%), and the disease control rate was 85.7% (95% CI, 67.4% to 104.0%). Eight patients died of ACC disease progression. *Table 2* summarizes the detailed outcome of each patient. Median PFS was 5.7 months (95% CI: 4.3 to not reached). Median OS was 23.4 months (95% CI: 12.9 to not reached; *Figure 2*).

Patients who achieved PR had a low P-TGR (*Figure 3*). P-TGR and tumor shrinkage% according to the RECIST 1.1 were positively correlated with a correlation coefficient of 0.56 (P=0.06; *Figure 4*). However, the sum of the target lesion before CAP chemotherapy was not correlated with the tumor shrinkage% (*Figure 5*).

Discussion

In this study, palliative CAP chemotherapy had a modest anti-cancer effect, with a response rate of 14.3% and median PFS of 5.7 months. A low P-TGR was associated with the response to CAP chemotherapy.

Chemotherapy for ACC was performed mainly for disease stabilization at the time of rapid progression of systemic metastasis. Anticancer drugs such as cisplatin, and 5-fluorouracil have been used alone or in combination to treat ACC (13-15). Several small-sized phase II studies have reported the effect of mitoxantrone, vinorelbine, paclitaxel, and gemcitabine (16-19). However, the overall response rate of these anticancer drugs for ACC is <20% (8,9,20). Although patients with salivary cancer treated with CAP showed a response rate of approximately 25–30%, all cases of salivary cancer not only ACC, were included, and only a few studies with ACC cases have been performed (15,21,22).

Table 2 Treatment and survival outcomes

No.	Age/Sex	Prior local treatment	Prior systemic treatment [line]	Time from diagnosis to CAP (months)	Cycle of CAP	Best response	Progression after CAP	Survival
1	48/F	Surgery, RTx.	Yes [1]	24.9	4	SD	Yes	Death
2	53/F	Surgery, RTx.	No	43.9	6	SD	Yes	Death
3	52/F	RTx.	No	1.8	6	SD	Yes	Death
4	39/M	Surgery, RTx.	Yes [1]	27.3	6	SD	Yes	Death
5	49/M	RTx., RFA	No	5.2	5	PR	Yes	Death
6	57/M	Surgery, RTx.	No	58.1	4	SD	Yes	Alive
7	49/M	RTx.	No	87.3	4	SD	Yes	Alive
8	46/F	No	Yes [1]	13.5	2	PD	Yes	Death
9	56/F	Surgery, RTx.	No	7.0	6	PR	Yes	Alive
10	45/M	Surgery, RTx.	No	72.6	6	SD	No	Alive
11	46/F	Surgery, RTx.	No	83.7	6	SD	No	Alive
12	48/M	Surgery, RTx.	Yes [4]	128.0	2	PD	Yes	Death
13	47/F	Surgery, RTx.	No	268.6	3	SD	No	Alive
14	55/F	Surgery, RTx.	Yes [1]	151.5	5	SD	No	Death

RTx, radiotherapy; CAP, cyclophosphamide, doxorubicin and cisplatin; PR, partial remission; SD, stable disease; PD, progressive disease.

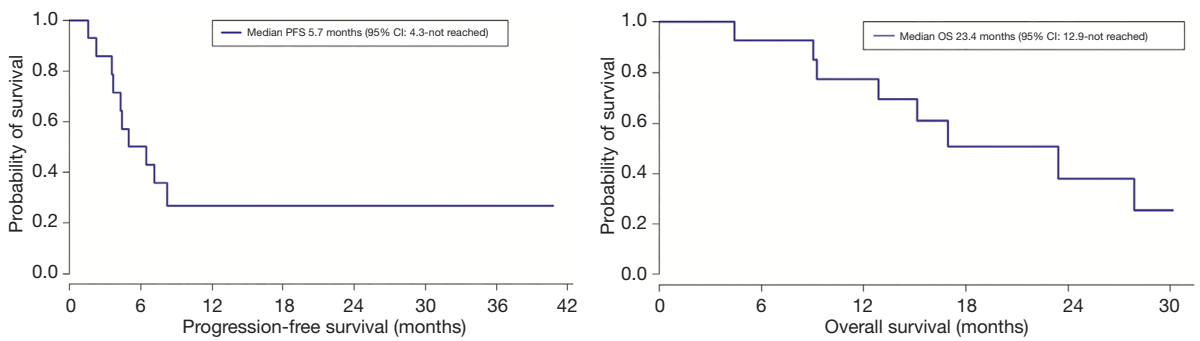

Figure 2 Progression-free survival and overall survival.

In the present study, only 2 of 14 patients achieved PR. However, 10 patients (71.4%) had stable disease without any severe adverse effects. Therefore, CAP combination chemotherapy may be considered for ACC treatment.

ACC is an indolent cancer, with patients showing symptoms after long periods. In some cases, patients with multiple metastasis showed long-term survival of >10 years (23-25). In patients with metastatic ACC without symptoms, there is no definite consensus for when to start systemic chemotherapy. Physicians often follow the wait-and-watch approach to determine the appropriate time for chemotherapy and initiate chemotherapy when the tumor starts growing rapidly. Thus, it is difficult to decide when to start chemotherapy for ACC patients. In our study, patients who had a lower P-TGR showed a good response to CAP chemotherapy. The patients who achieved PR were treatment naïve patients and two patients with PD were took systemic chemotherapy before CAP chemotherapy. Three of five patients who treated with other systemic chemotherapy were experienced SD. Although previous treatment is not consistent, our study suggests that early initiation of chemotherapy for patients with a low P-TGR

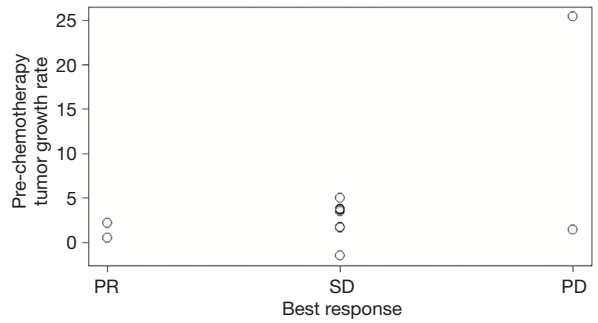

Figure 3 Pre-chemotherapy tumor growth rate and best response of cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy.

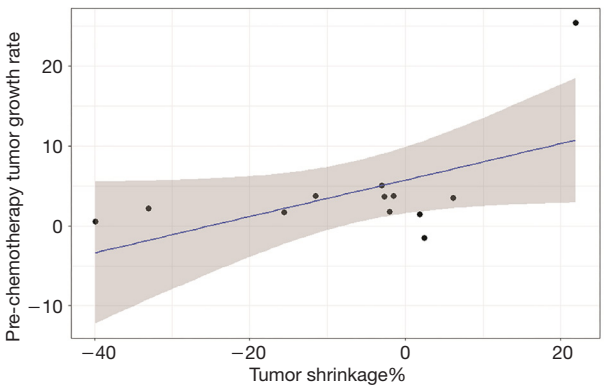

Figure 4 Pre-chemotherapy tumor growth rate before cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy and tumor shrinkage% after CAP chemotherapy.

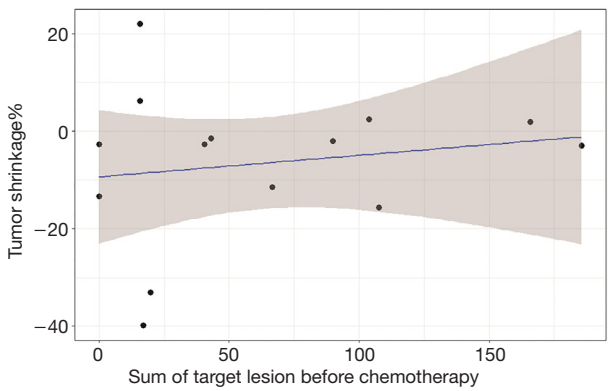

Figure 5 Sum of target lesion before cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy and tumor shrinkage% after CAP chemotherapy.

may be more helpful for disease control.

Our study has several limitations. This was a single-center retrospective study, with a small number of patients. Moreover, the prior administered treatments varied between patients.

Nevertheless, considering the rare incidence of ACC, it is difficult to conduct a randomized phase III trial for evaluating the effect of chemotherapy. Our study confirmed the effect of CAP chemotherapy for ACC and determined the relationship between the P-TGR and treatment response. Owing to the limited research about when chemotherapy for ACC should be started, this study has the strength of being able to determine the timing for the initiation of chemotherapy. However, further studies are needed to determine the role of CAP chemotherapy and prognostic factors under homogeneous clinical conditions.

In conclusion, the results of this study suggested that CAP chemotherapy might be a suitable treatment option for ACC. A low P-TGR was associated with a good response to CAP chemotherapy. Early initiation of chemotherapy could be helpful to control metastatic ACC, although the appropriate timing of chemotherapy should be considered carefully.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco.2020.03.07). BK serves as an unpaid editorial board member of *Chinese Clinical Oncology* from Mar 2019 to Feb 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was reviewed and approved by the Institutional Review Board of SNUH (approval number: H-1812-059-993).

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