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Original Article

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Clinical Features and Treatment of Collecting Duct Carcinoma of the Kidney from the Korean Cancer Study Group Genitourinary and Gynecology Cancer Committee

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Purpose

Collecting duct carcinoma (CDC) of the kidney is an aggressive disease with a poor prognosis, accountings for less than 1% of all renal cancers. To date, no standard therapy for CDC has been established. The aim of this study is an investigation of clinicopathologic findings of CDC and correlation of the disease status with a prognosis.

Materials and Methods

From 1996 to 2009, 35 patients with CDC were treated at eight medical centers. The diagnosis of CDC was made based on nephrectomy in 27 cases and renal biopsy in eight cases.

Results

Median PFS and OS for all patients were 5.8 months (95% CI 3.5 to 9.2) and 54.4 months (95% CI 0 to 109.2), respectively. The OS of patients with Stages I-III was 69.9 months (95% CI 54.0 to 85.8), while that of patients with Stage IV was 8.6 months (95% CI 0 to 23.3), which showed a statistically significant difference (p=0.01). In addition, among patients with Stage IV, the OS of patients who received a palliative treatment (immunotherapy, chemotherapy, or targeted therapy) was 18.4 months, which was higher than the OS of patients without treatment of 4.5 months.

Conclusion

CDC is a highly aggressive form of renal cell carcinoma. Despite most of the treatments, PFS and OS were short, however, there were some long-term survivors, therefore, conduct of additional research on the predictive markers of the several clinical, pathological differences and their treatments will be necessary.

Key words
Renal cell carcinoma, Kidney, Treatment, Prognosis

Introduction

Collecting duct carcinoma (CDC) of the kidney is an unusual variant of renal cell carcinoma (RCC), accountings for less than 1% of all renal cancers [1]. CDC arises precisely from the principal cells lining distal collecting ducts of epithelium and distal renal tubules that originates from mesonephros [2,3]. Considering that urothelial carcinoma originating from the ureter, pelvis, or calices also arises from the mesonephros, CDC might be similar to urothelial carcinoma and its radiologic and pathologic findings differ from those of other RCCs. Recent publications have pointed out the histological heterogeneity of this neoplasm and its extensive histological overlapping with high grade papillary tumors and urothelial carcinoma [4]. Accurate diagnosis is important for proper management. In diagnosis of CDC, it is important to distinguish between invasive papillary RCC and urothelial carcinoma. Positive immunohistochemical staining for distal tubules and collecting duct markers is helpful indiscrimination of CDC from the more commonly diagnosed clear cell RCC of proximal nephron origin [5]. CDC generally expresses broad spectrum keratins and high molecular weight (HMW) cytokeratin, which is expressed in the lower nephron and the urothelium. It also shows positive staining with E-cadherin, epithelial membrane antigen, CKβE12, and CK19. However, CD10, c-KIT, and a-methylacylCoA racemase (AMACR) show no staining. In contrast, papillary RCC showed positive results for CD10 and AMACR, and it appears to be different from CDC [6]. However, this immunohistochemistry is not specific and may be seen in medullary carcinomas and in urothelial carcinoma, including those arising in the renal pelvis [7]. Charaterization of CDC is difficult due to its low incidence. Although the gross and microscopic features of the tumor are well established, diagnostic confusion can still occur.

The most common presenting symptoms include gross hematuria, pain, and general weakness. CDC is also found with a palpable abdominal mass on physical examination. CDC presents clinical features similar to those of other RCCs. However, lymph node metastasis and distant metastasis occur more frequently in CDC. CDC is an aggressive disease with a poor prognosis. At diagnosis, 40% of patients have already developed metastatic lesions, including lymphnodes, lungs, or adrenal glands [2,8]. Clinical outcome is poor, with 66% of patients dying of the disease within two years after diagnosis [9]. Various treatments have been proposed, including radiation therapy, immunotherapy, and some combinations of chemotherapy, however, results have been unsatisfactory.

To date, no standard therapy for CDC has been established. The aim of this study is to conduct an investigation of the clinicopathologic findings of CDC and to determine their correlation with the disease status and prognosis.

Materials and Methods

We retrospectively reviewed 35 patients diagnosed with CDC at eight Korean medical centers from 1996 to 2009. Data on gender, age, initial symptoms, and laboratory findings, including complete blood count profile, calcium, and urine analysis, pathological features, treatment, and patient outcome were obtained from patient medical records. Diagnosis of CDC was made by examination of a nephrectomy specimen in 27 cases and by renal biopsy in eight. Pathological studies included light microscopy and immunohistochemistry. Tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM stage classification. Patient outcome was assessed by computed tomography. This study was approved by the Institutional Review Board (IRB) from each participating institution.

Tumor response after treatment was re-evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.0) [10]. Progression free survival (PFS) was estimated from the date treatment began to the date when disease progression was recognized, or the date of the last follow-up visit, or the date of death. Overall survival (OS) was estimated from the date of diagnosis to the date of death from

Table 1. Patients' characteristics

Characteristic	No. (%) (n=35)
Median age	56 (29-82)
Gender (%)	
Male	25 (74)
Female	10 (26)
ECOG performance status	
0-1	31 (88)
2	4 (12)
Initial symptoms (%)	
Asymptomatic	3 (9)
Symptomatic	32 (91)
Pain	16 (44)
Hematuria	14 (39)
Weight loss	5 (14)
Palpable mass	1 (3)
Median hemoglobin (g/dL)	12.5 (8.9-18.3)
Median calcium (g/dL)	9.3 (7.9-11.1)

Values are presented as number (range or %). ECOG, Eastern Cooperative Oncology Group.

Table 2. Tumor characteristics

Characteristic	No. (%) (n=35)
Tumor size (cm)	
<7	17 (49)
≥7	10 (29)
Unknown	8 (22)
Lymph node status by imaging or surgery	
N0	0 (0)
N1	18 (51)
N2	12 (34)
Unknown	5 (15)
TNM stage (AJCC 6th)	
Stage I	9 (26)
Stage II	2 (6)
Stage III	4 (11)
Stage IV	19 (54)
Unknown	1 (3)
No. of metastasis sites	
1	8 (23)
2 or greater	8 (20)
Metastasis site (%)	
Bone	9 (26)
Lung	8 (23)
Lymph nodes	3 (9)
Liver	2 (6)
Others	1 (3)

AJCC, American Joint Committee on Cancer.

any cause or the last follow-up visit.

OS and PFS were estimated using the Kaplan-Meier product-limit method. Survival rates were compared for statistical differences using log-rank analysis. The Cox regression model was used for multivariate analysis with factors that had been used in univariate (log rank) analysis of OS and PFS. All statistical analyses were performed using the SPSS ver. 14.0 (SPSS Inc., Chicago, IL) for Windows. p-values less than 0.05 were considered statistically significant and all p-values correspond to two-sided significance tests.

Results

A list of patient and tumor characteristics is shown in Tables 1 and 2. The median age of patients was 56 years (range, 29 to 82 years) and 74% of the patients were male. Of 32 symptomatic patients, 16 and 11 experienced pain and gross hematuria. Other presenting symptoms included weight loss, microscopic hematuria, and a palpable mass. Seventeen patients had a tumor size of 7 cm or less, and 10 patients had a tumor size of 7 cm or greater. The median level of hemoglobin and calcium was 12.5 g/dL (range, 8.9 to 18.3 g/dL) and 9.30 g/dL (range, 7.9 to 11.1 g/dL), respectively. According to the immunohistochemistry finding, CDC expressed cytokeratin in nine patients (26%), HMW-cytokeratin in 14 (40%), low molecular weight-cytokeratin in three (8.6%), and CKβE12F in one (2.9%). It also expressed CD10 in five (14.3%) and vimentin in 11 (31.4%). At diagnosis, nine, two, four, and 19 patients had TNM stage I, II, III, and IV, respectively. Eight patients had two or more metastatic sites of the bone (44%), lungs (39%), liver (16%), and lymph nodes (11%) as the most common sites.

With a median follow-up period of 15.8 months (range, 0.6 to 88.4 months), 14 (40%) deaths were reported. During the median follow-up period of 15.8 months, 14 patients died, while nine patients (25.7%) were lost in the follow-up. Twenty seven of the 35 patients underwent nephrectomy for initial treatment (curative surgery in 17, and palliative in 10), three patients received chemotherapy, and four patients did not receive any treatment (Fig. 1). Palliative chemotherapy was administered for 22 persons, who were composed of eight of 14 relapsed patients, eight of 10 patients who were in stage IV and underwent palliative surgery, and four patients who did not undergo an operation (Fig. 1). The types of palliative treatment administered to patients are shown in Fig. 1. Median PFS and OS for all patients were 5.8 months (95% confidence interval [CI], 3.5 to 9.2 months) and 54.4 months (95% CI, 0 to 109.2 months), respectively (Figs. 2 and 3A). The OS of the patients with stages I-III was 69.9 months (95% CI, 54.0 to 85.8 months), while that of patients with stage IV was 8.6 months, which showed a statistical significant difference (p=0.01) (Fig. 3B). In addition, among patients with stage IV, the OS of patients who received a palliative treatment (immunotherapy, chemotherapy, or targeted therapy) was 18.4 months, which was higher than the OS of patients without treatment of 4.5 months. The PFS of patients with stages I-III was 6.9 months (95% CI, 1.3 to 12.4 months). Recurrence occurred in 14 patients, 82% of the 17 patients who underwent a curative surgery, and their average recurrence period was 5.9 months, with a short PFS and a high relapse rate.

Using the log-rank method, no relationship was demonstrated between survival end points (PFS and OS) and explanatory covariates, including patients' age, gender, and initial calcium level, except for hemoglobin (p=0.005 and p=0.193, respectively) and initial TNM stage (p=0.022 and p=0.002, respectively). Results of multivariate regression analysis using a Cox's proportional hazards model showed that TNM stage (I-III vs. IV; hazard ratio, 4.58; 95% CI, 1.301 to 16.135; p=0.018) was an independent prognostic factor for survival of CDC (Table 3).

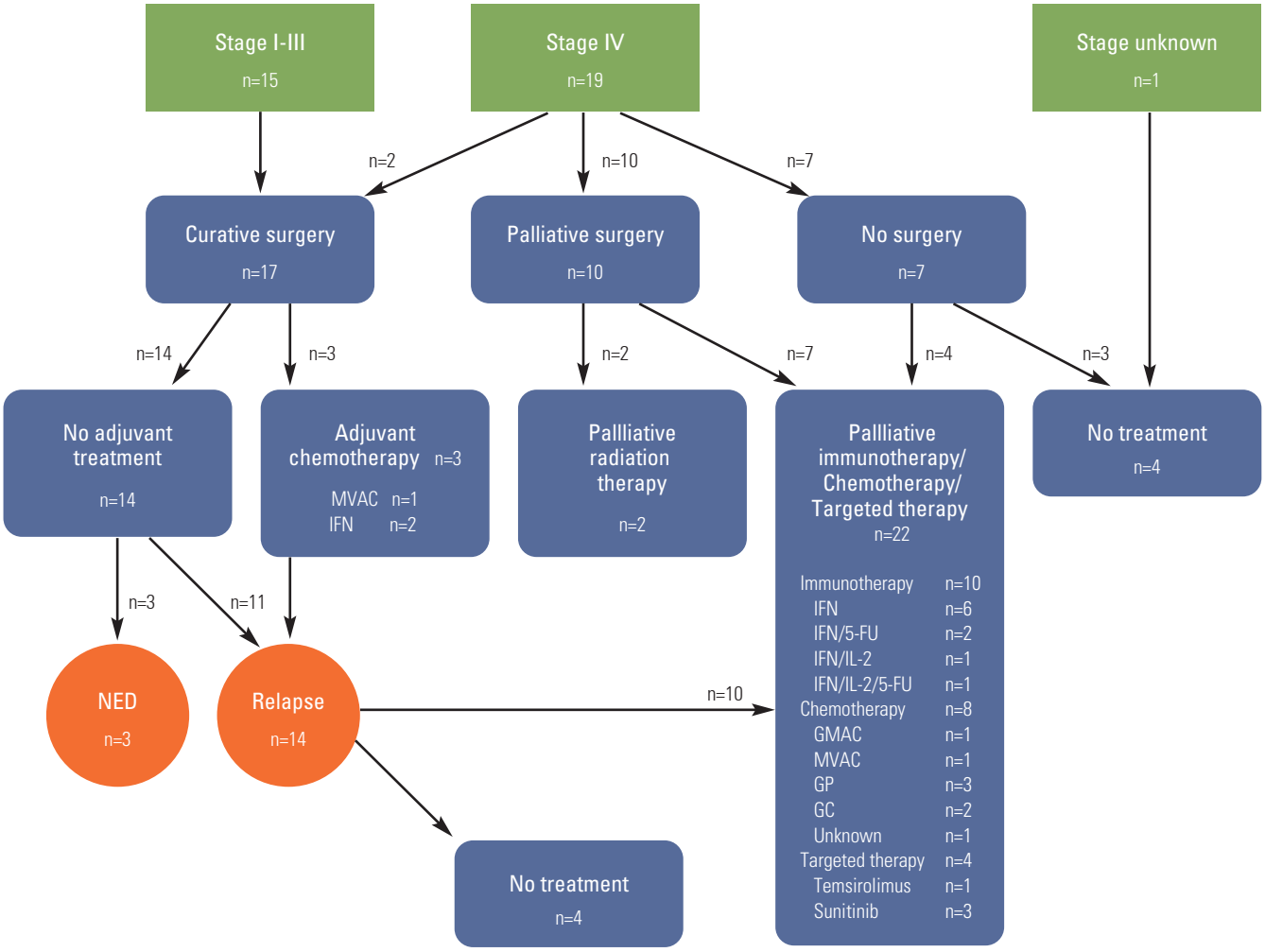

Fig. 1. Summary of treatment results. MVAC, methotrexate, vinblastin, Adriamycin, and cisplatin; IFN, interferon; NED, no evidence of disease; 5-FU, 5-fluorouracil; IL-2, interleukin-2; GMAC, gemcitabine, methotrexate, Adriamycin, and cisplatin; GP, gemcitabine and cisplatin; GC, gemcitabine and carboplatin.

Table 3. Multivariate analysis for overall survival

Statement	p-value	Hazard ratio	95% Confidence interval
T	0.45	0.68	0.25-1.84
N	0.45	0.84	0.19-3.73
Size (<7 cm vs. ≥7 cm)	0.92	1.13	0.09-13.73
Stage (I-III vs. IV)	0.03	49.58	1.55-1,584.01
Age (<50 yr vs. ≥50 yr)	0.74	1.34	0.24-7.44
Hb (12 g/dL vs. ≥12 g/dL)	0.43	1.20	0.38-10.50
Ca (10 mg/dL vs. ≥10 mg/dL)	0.46	1.77	0.40-7.90

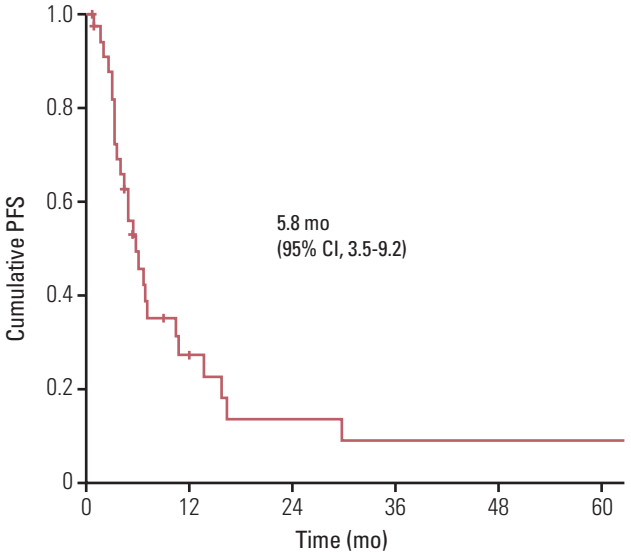

Fig. 2. Progression free survival (PFS) for all patients. CI, confidence interval.

Discussion

CDC of the kidney is known to be a rare and unique disease. The frequency of CDC is within 1% of the entire RCC and its radiologic and pathologic findings differ from those of other RCCs. In 1976, Mancilla-Jimenez et al. [11] reported on 34 cases of papillary RCC and postulated a collecting duct origin for three of these tumors based on the findings of atypical hyperplastic changes in adjacent collecting tubules. In Korea, several CDCs have been reported in the literature [12-14]. This is the first report on CDC based on medical records from eight institutions in Korea. In Japan, a retrospective survey was conducted in order to analyze the nature of CDC [15]. In the study, the central pathologists confirmed CDC in 81 of 120 cases diagnosed as CDC at 66 institutions. It was a large-scale nationwide survey with an advantage of a multi-institutional central review. However, there were no outcome reports on the responses for each treatment. On the other hand, in this study, 35 patients were selected from eight different organizations nationwide in Korea. Although a pathological central review was not performed, there was significant detailed information on each case with the pattern of cases and treatment outcomes. Thus, based on such information, the results were evaluated with regard to the types of post operational treatment and the drugs used as palliative treatment and the responses.

Our results are in agreement with those of previous reports showing that the median age was 56 years (range, 29 to 82 years) and that males comprised 74% of the patient population. In our study, CDC expressed cytokeratin, HMW-cytokeratin, and CKβE12 in many cases, however, it also expressed CD10 and vimentin, which is generally expressed in the upper nephron, and not in the lower nephron. Ninety-one percent of patients had symptoms and the most common presenting symptoms were pain, hematuria, and weight loss. At diagnosis, 19 (54%) patients were TNM stage IV, and the median OS period of patients with stage IV was 9.29 months

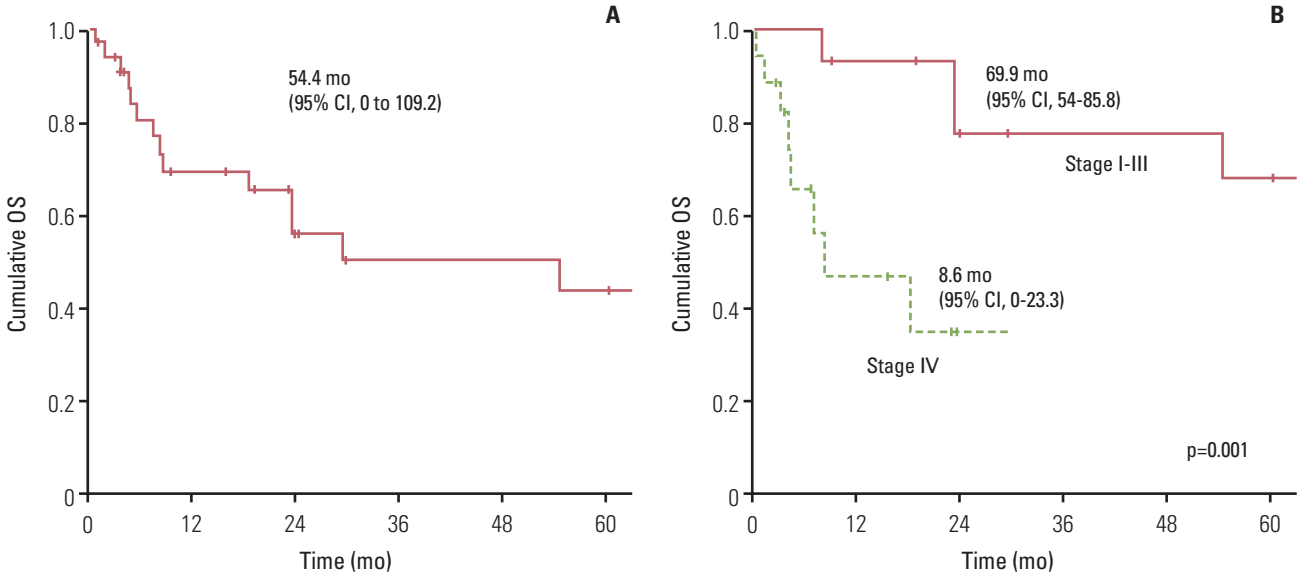

Fig. 3. Overall survival (OS). (A) OS for all patients. (B) OS for patients with stage I-III (red) and IV (green). OS, overall survival; CI, confidence interval.

(95% CI, 0.0 to 26.78 months).

A summary of the clinical data on CDC gathered from published series and case reports is shown in Table 4. Due to the rarity of its occurrence, optimal treatment for CDC has not been established. Despite past reports on striking responses to cytokines, currently, immunotherapy only has an historical role. CDC might be distinct from conventional RCC and share embryological origins and biological features with urothelial carcinoma. Therefore, even if trials comparing immunotherapy with chemotherapy have not been conducted, chemotherapy currently represents the most used therapeutic approach. However, it remains unclear whether this carcinoma should be managed with a treatment similar to that for urothelial cell carcinoma or RCC. Multiple chemotherapeutic and/or immunotherapeutic regimens have been tried for treatment of CDC (Table 4). These data appear to suggest that chemotherapy and immunotherapy may offer only limited benefits to a selected group of patients.

In our study, surgical treatment was performed as the initial treatment in 77% of patients. However, recurrence occurred in most patients who underwent surgery and a palliative treatment was administered in 75% of patients. Most patients with advanced or recurrent disease were treated with immunotherapy, chemotherapy, radiation therapy, or targeted therapy. The most commonly used agents included interferon, gemcitabine, cisplatin/carboplatin, and sunitinib. The total OS was 54 months, while the PFS was only 5.8 months. It seems that patients with stages I-III had a high relapse rate with a short PFS of 6.9 months, while seven patients (58%) with stages I-III survived for a long time with patients in the no evidence of disease state, contributing to the increase of the OS, so that there was a discrepancy between the PFS and the OS. Most of the long-term survivors were in stages I-III and those who received palliative treatment after a relapse, and the treatments administered to these patients included target therapy as well as immunotherapy and chemotherapy. Due to the small number of patients, the correlation between the prognosis and the treatment could not be known. However, it can be assumed that palliative treatment takes the role of extending survival. In paticular, the current standard therapy against RCC is the targeted therapy, and though it is recognized as a different disease from RCC, there were some CDC patients who were treated with sunitinib, temsirolimus, or other targeted agents, different from the past.

According to an analysis of clinical aspects, treatment and prognosis in the records of seven CDC patients diagnosed

Table 4. Summary of previous reports for treatment modalities and therapeutic regimens

References	Initial treatment	Major therapeutic regimens	Survival
Dimopoulos et al. [8]	Surgery Chemotherapy Immunotherapy	MVAC 5-FU/IFN-α/MMC IL-2/IFN-α	1 NED (30 mo) 1 minor response (5 mo) 3 SD (10, 15, and 16 mo) Median survival 22 mo
Chao et al. [16]	Surgery	Paclitaxel/carboplatin	2 NED (<1 mo, 5 yr) 4 died (7-17, average 11.5 mo)
Peyromaure et al. [17]	Surgery	IFN-α Prednisolone Gemcitabine/cisplatin	4 NED (9, 13, 17, and 27 mo) 2 died (5, 24 mo) 3 loss
Mejean et al. [18]	Surgery	IFN-α	2 NED (99, 100 mo) 8 died (3 postop, 6-21 mo)
Tokuda et al. [15]	Surgery	Immunotherapy Chemotherapy	1, 3, 5, and 10-yr survival 69.0%, 45.3%, 34.3%, and 13.7%
Oudard et al. [9]	Surgery Chemotherapy	Gemcitabine/platinum	Median OS 10.5 mo
Present study	Surgery (curative 17, palliative 10) Chemotherapy	Immunotherapy Gemcitabine/platinum MVAC, GMAC Sunitinib, temsirolimus	4 NED (81.7-88.8, median 88.2 mo) 8 alive with disease (19.1-82.6, median 26.9 mo) 14 died (0.63-54.37, median 7.8 mo) 9 loss

MVAC, methotrexate, vinblastin, Adriamycin, and cisplatin; NED, no evidence of disease; 5-FU, 5-fluorouracil; IFN, interferon; MMC, mitomycin C; IL-2, interleukin-2; SD, stable disease; OS, overall survival; MVAC, methotrexate, vinblastin, Adriamycin, and cisplatin; GMAC, gemcitabine, methotrexate, Adriamycin, and cisplatin.

with RCC in Procopio's study and included in patients treated with the target therapy, five persons showed survival of four months while two patients showed long-term survival of 49 months and 19 months, respectively [19]. In this study of the patients who were recently diagnosed and received a target therapy, one patient for whom sunitinib was used finally died, but showed a partial response during treatment.

CDC is an aggressive disease with poor prognosis, however, like some patients in this study who survived for a long period of time, a study on predictive markers by which the outcomes of prognosis and therapy, especially target therapy as well as their clinical features can be predicted is needed.

Conclusion

CDC is a highly aggressive form of RCC. Despite most of the treatments, PFS and OS were short, however, there were some long-term survivors, therefore, additional research on the predictive markers of several clinical, pathological differences and their treatments will be needed.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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