Treatment of Collecting Duct Carcinoma: Current Status and Future Perspectives

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Abstract. *Background: Chemotherapy for collecting duct carcinoma (CDC) has demonstrated only limited efficacy in the advanced setting. The present study evaluated the activity of targeted therapies in metastatic CDC. Patients and Methods: We evaluated a cohort of 384 consecutive patients with metastatic renal cell carcinoma (mRCC). The characteristics of patients with CDC were compared against those of the remaining cohort. All patients with CDC were treated with targeted therapies. Results: Thirteen patients with advanced CDC were referred to our Center (incidence: 3.4% of all mRCC). Median age was 57 and 62 years in the CDC and non-CDC groups, respectively. The overall disease control in the CDC population was 23%, and median overall survival was 4 (95% confidence interval(CI)=2.4-5.6) months. Three patients obtained a satisfying response (disease control lasting 6-33 months). Conclusion: CDC has a poor prognosis compared to non-CDC renal cell carcinoma. Treatment for CDC represents a future challenge and targeted therapies may play a role in selected cases.*

Carcinoma of the collecting ducts of Bellini (CDC) is a rare and aggressive renal disease first described in 1949 (1). This is a particular entity separate from clear cell renal cell carcinoma since it derives from the distal nephron and arises from the epithelial layer of distal tubules, which is more similar to the urothelial cells than to renal cells (2).

CDC affects approximately 1% of patients with renal cancer, and to date, solely 100 cases of this disease have been documented (2). Clinically, patients affected by CDC have a median age of 55 years and are male, CDC occurring at a male:female ratio of 2:1. Most frequent symptoms of CDC are abdominal pain, flank mass and hematuria.

The diagnosis of CDC is challenging. From a radiological point of view, CDC arises as a central medullar renal mass with a minimal contrast capture, this reflecting the modest vascularization of the tumor (Figure 1). Satellite nodes can also be found in the renal cortex; a cortical localization has been also described, but is rare (3). Imaging of the upper tract often suggests urothelial carcinoma, and urine cytology may occasionally be positive (4, 5). Typically, central renal masses are diagnosed as clear cell and papillary tumors that rarely arise from the proximal tubules localized in the Bertini columns (3). This peculiar localization also explains, at least in part, the difficulties in diagnosing centrally-located CDCs.

About one-third of patients with CDC present with metastases, and the cancer-specific survival for all stages at one and three years is 69% and 45%, respectively (6). This low survival rate is also related to the lack of effective medical therapies for metastatic disease. In fact, treatments were historically-chosen based according to its common origin with urothelial cancer; however chemotherapy regimens used for bladder cancer have led to disappointing results. Immunotherapy has only a limited role, while anti-angiogenic agents hold promise for selected patients (7).

The aim of this analysis was to evaluate the efficacy of anti-angiogenic therapies for advanced CDC.

Patients and Methods

Medical records of patients affected by kidney tumor without transitional cell histology treated at our Institution – Istituto Nazionale Tumori (Milan, Italy), the reference Center for the treatment of oncological diseases in Northern Italy - from December 2006 to January 2013 were reviewed and all cases of CDC were selected. Written informed consent to participate in the study was obtained from each patient before entering the study. The study protocol was approved by the Local Ethical Committee and the investigation conforms to the principles outlined in the Declaration of Helsinki. All cases were reviewed by an internal pathologist and only confirmed cases of CDC were considered for further analysis. No inclusion/exclusion criteria were applied.

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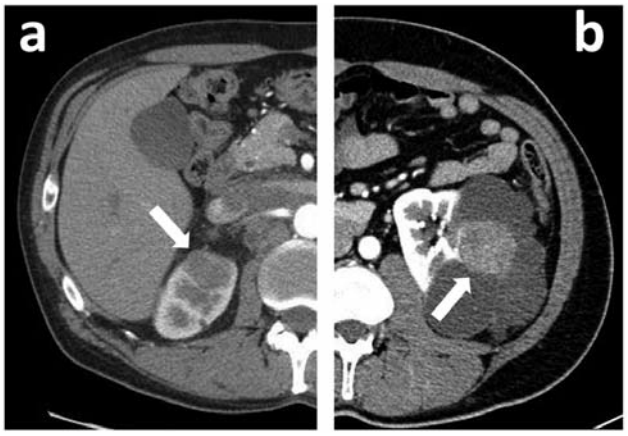

Figure 1. *Radiographic aspect of primary collecting duct carcinoma (arrow) arising centrally (a) or among cystic lesions of the kidney (b). Both images are characterized by a minimally-contrast capture reflecting the low vascularization of the tumor.*

Table I. *Main characteristics of patients at baseline.*

Characteristic	CDC Pts (N=13)	Non-CDC Pts (N=371)
Median age (range) years	57 (33-79)	62 (25-82)
Gender		
Male	10 (77%)	271(73%)
Female	3(23%)	100 (27%)
ECOG performance status		
0	8 (61%)	202 (55%)
1	4 (31%)	147 (40%)
2	1 (8%)	22 (6%)
Previous nephrectomy		
Yes	11 (85%)	334(90%)
No	2 (15%)	50(13%)
Sites of disease		
Lymph nodes	11 (85%)	144 (39%)
Lung	3 (23%)	251 (67%)
Bone	3 (23%)	105 (28%)
Liver	2 (15%)	72 (19%)
No. of sites of disease		
1	7 (54%)	140 (38%)
≥2	6 (46%)	231 (62%)

For each patient the following data were recorded: gender, age at diagnosis, date of nephrectomy, stage of disease at diagnosis, site of metastases, treatment response and outcome. Therapies were all started at standard dose and recommended dose reductions were applied in the case of toxicity, according to summaries of product characteristics.

Outcomes measurement and statistical analysis. The characteristics of CDC were compared against those of non-CDC. Only patients with CDC were considered for the efficacy analysis, which comprised the evaluation of radiological response to therapy and overall survival (OS). Response to therapy was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) carried out according to local procedures every 8-12 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (8). The OS was defined as the time from the beginning of treatment to death (or last contact).

All data were analyzed by descriptive statistics. OS was estimated using the Kaplan–Meier method with Rothman's 95% confidence intervals (CI) and compared across the groups using the log-rank test. A p-value of less than 0.05 was considered statistically significant. PASW (Predictive Analytics SoftWare) (v19; IBM SPSS, Chicago, IL, US) was used.

Results

Patients. A total of 384 patients were considered in the analysis; in total, 13 patients were affected by CDC, with an incidence of 3.4%.

In the overall population, the median age was 62 (range=25-82) years, with a male:female ratio of 3:1. Clear cell histology was the most frequent, representing approximately 86% of cases, while the remaining 14% of cases were non-clear cell tumors (including the 13 cases of CDC).

The main characteristics of patients with CDC are summarized in Table I. Symptoms were present in 72% of patients, with gross hematuria and abdominal pain being the most frequent. Twelve patients had metastatic disease at diagnosis and one developed metastases after a disease-free period of five months. Eleven patients underwent palliative nephrectomy, while the remaining two were diagnosed by biopsy of the renal mass or the supraclavicular metastasis.

The median survival for the CDC cohort was 4.0 (95% CI=2.4-5.6) months; by way of a qualitative-only comparison, the median OS in non-CDC patients was 24 (95% CI=20.4-27.6) months.

Treatment efficacy. In the first-line setting, two patients received temsirolimus, seven sorafenib, three sunitiniband one pazopanib. Treatment was selected on the basis of the Memorial Sloan-Kettering Cancer Center prognostic criteria, the general status of each patient, and the specific toxicity profile of each drug.

Three patients obtained a satisfying response to treatment: one patient treated with sorafenib, one with sunitinib and one treated with temsirolimus; disease control lasted for 33, 8 and 6 months, respectively. The same three patients, at the failure of first-line treatment, were offered a second-line: the two patients in whom disease progressed after sorafenib and temsirolimus received sunitinib, and the patient whose disease progressed with sunitinib received everolimus. OS for the two patients treated with the sorafenib-sunitinib and the temsirolimus–sunitinib sequences was 49 and 19 months, respectively.

Table II. *Efficacy and treatments in the five patients responding to targeted therapy (TT).*

	First-line treatment			Subsequent treatment	
TT	Best disease control achieved	Duration (months)	TT	Best disease control achieved	Duration (months)
Tem	SD	6	Su	PR	9
Su	SD	8	Ev	SD	3 +
So	PR	33	Su	PR	10
So	SD	4	Su	SD	3 +
Su	SD	3+			

Tem: Temsirolimus; Su: sunitinib; So: sorafenib; SD: stable disease; PR: partial response (according to RECIST 1.1); NA: not assessed; +: treatment ongoing.

To date, three patients are still alive; one patient is receiving first-line therapy with sunitinib, while two are receiving second-line treatment (everolimus and sunitinib, after sunitinib and sorafenib failure, respectively). The remaining eight patients experienced early disease progression during the first-line therapy, with an OS ranging from 1 to 4 months. Efficacy of the treatment is summarized in the Table II.

Most common adverse events reported during targeted therapy included fatigue, diarrhea, hand-foot syndrome, hypertension and anemia. Almost all adverse events were of mild severity, with only one patient experiencing a moderate hand-foot syndrome which required one week of treatment (sorafenib) discontinuation.

Discussion

CDC is a very aggressive disease, characterized by poor prognosis, and by a difficult-to-assess incidence due to its rarity. In the present study, CDC accounted for 3.4% of kidney neoplasms treated for metastatic disease in a reference center. The increased number of cases with CDC histology with respect to previous reports in our opinion could be attributed, at least in part, to the fact that our Institution is a reference center for rare tumors.

Tumor spread is characterized by metastasis to nodes, lungs, bone and liver. Our analysis reports the nodal involvement to be more frequent in CDC compared with other renal tumors, while lung metastases were less frequent.

In addition, we report that the prognosis of CDC was poorer than that for other renal tumors treated at our Institution. Previous experience was not unequivocal in terms of prognosis and chemotherapy efficacy (5, 9).

The poor prognosis of CDC may be related to the lack of therapies able to control tumor growth. Most reports have tested some chemotherapy-based regimens which included methotrexate, vinblastine, doxorubicin and cisplatin, platinum-based doublets and gemcitabine, or paclitaxel (9). In the largest retrospective experience reported to date, only 17 out of 49 patients received chemotherapy, while the others received immunotherapy, radiotherapy or surgery. Unfortunately, in this cohort, only 26 patients had metastatic disease and the activity of chemotherapy in reducing tumor growth was not reported (9).

Moreover, because of its rarity, CDC has always been excluded from randomized trials evaluating chemotherapy or targeted therapies for urological tumors. To date, only the prospective BELLREIN phase II trial, conducted by the GETUG French group, has been published (10). This study evaluated the efficacy and safety of cisplatin or carboplatin plus gemcitabine as upfront therapy in 23 patients with advanced CDC. The final results of the study have been disappointing in terms of efficacy in particular if compared with current survivals from other renal neoplasm: median progression-free survival and OS were 7.1 and 10.5 months, respectively (10).

Recently, we showed the activity of targeted therapies for the treatment of advanced CDCs (11), and with the present analysis, we documented the efficacy of these agents in selected cases. However, the response to anti-angiogenic or inhibitors of the mammalian target of rapamycin was not the same among the studied participants, suggesting poor knowledge of the biology of this tumor type. In fact, the different tumor spread and prognosis reported in our cohort is probably due to some differences in the origins of the tumors.

Different patterns of genetic alterations have been described between CDC and the most frequent clear cell histology. The first is characterized by loss in the chromosome 1q, 6p, 8p, 14, 18 and 22, while clear cell carcinoma is mainly characterized by gain in chromosome 5q and loss of 3p, 6q, 8p, 9p and 14q (12). Moreover, similarly to urothelial cancer, overexpression/amplification of human epidermal receptor-2 (HER2) was reported in CDC (13, 14). The presence of this target may be promising for the evaluation of HER2-targeted therapies such as antibodies lapatinib or trastuzumab. Even if the results of these agents in urothelial cancer were disappointing, Bronchud *et al*.

demonstrated a good and long-lasting clinical and radiological response with a double-HER2 blockade in a young patient with advanced CDC showing marked HER2 positivity (14).

In conclusion, our study may suggest three main findings: first, a greater incidence of CDC than that previously reported in literature among patients affected by metastatic renal tumors; second, the poor prognosis of patients with metastatic CDC; and third, the potential efficacy of targeted therapies in this setting. However, several limitations should be taken into account, including the retrospective nature of the analysis and the low number of patients evaluated.

We believe that a better knowledge of CDC biology and a cooperative effort to design prospective trials might further elucidate the role of targeted therapies for treatment of this tumor in the near future.

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