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Tumour Review

Collecting ducts carcinoma: An orphan disease. Literature overview and future perspectives

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ABSTRACT

Collecting ducts carcinoma (CDC) is a rare and aggressive histological subtype of renal cancer accounting for only 1% of renal tumors. Usually patients present in bad clinical conditions due to a symptomatic disease with synchronous metastasis. Due to the rarity of CDC, data from prospective trials evaluating the best treatment for these patients are limited. The prognosis is poor with a median overall survival of around 11 months for patients with metastatic disease. The best treatment option today is considered a doublet chemotherapy with platinum salt plus gemcitabine as a result from a prospective phase II trial, but survival outcomes remain unsatisfactory.

The interest in the in-depth understanding the biology of this orphan disease is growing, leading to find potential new biological-driven treatment approaches. Here we review the up-to-date literature evidences to address the best management of this rare and unfavorable clinical condition.

Introduction

Collecting ducts carcinoma is a malignant epithelial tumor arising from the principal cells of distal segment of the collecting ducts of Bellini in the renal medulla [1]. CDC is a rare tumor, accounting for only 1% of renal tumors with distinct clinical, histological and pathological characteristics [2–4], first recognized by Mancilla-Jimenez et al. in 1976 [5] and then further described by Fleming and Lewi in 1986 [6].

The 2012 ISUP Vancouver [7] and 2016 WHO classification [1] established several diagnostic criteria for this tumor: at least a portion of the tumor involves the medullary region; predominant formation of tubules; desmoplastic stromal reaction; cytological high-grade features; infiltrative growth patterns; no other renal cell carcinoma (RCC) subtypes or urothelial carcinoma. The main differential diagnoses of CDC are invasive urothelial carcinoma of the upper urinary tract with whom it shares the embryological origin from mesonephric [8], renal medullary carcinoma, fumarate hydratase-deficient RCC, type 2 papillary RCC, unclassified RCC, adenocarcinoma of the renal pelvis, and metastatic carcinoma [1,9].

Due to the rarity of CDC and complexity in the diagnostic criteria, facing the suspect of CDC diagnosis, a histological review with a dedicated pathologist is strongly recommended.

The first large CDC case series consists of 81 confirmed CDC cases diagnosed at 66 Japanese Institutions. Of note, the dedicated pathology review excluded 39 among the 120 identified as CDC due to misdiagnosis, primarily with papillary RCC. 65.4% of patients presented a symptomatic disease, 44.2% had lymph node and 32.1% metastatic dissemination. Survival rates were poor with 3, 5 and 10-year disease specific survival of 69.0%, 45.3%, 34.3% and 13.7%, respectively [10].

A multicentric European and Nord-American collaboration identified 5346 RCC and 41 CDC patients within a cohort of 6608 patients treated with either radical or partial nephrectomy for renal cancer. Again, aggressive peculiarities, like higher grade and stage together with a more symptomatic disease at presentation, were detected more frequently in CDC than RCC patients [11].

While the majority of patients with CDC display a dismal prognosis, a subset has excellent survival. Results from a retrospective study that retrieved records from 95 CDC patients that received radical or partial nephrectomy, identified clinical and pathological parameters that enable the prediction of disease specific mortality. In detail, American Society of Anesthesiologists (ASA) score 3–4, tumor size greater than 7 cm, stage M1, Fuhrman grade 3–4 and lymphovascular invasion independently predicted disease specific mortality. The authors generated a risk-score from these variables, classifying patient at low, intermediate and high risk with a 5-year disease specific survival rate of

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96%, 62% and 8%, respectively [12].

Among 11 CDC patients, Taguchi et al. described another independent negative prognostic marker. A neutrophil-to-lymphocyte ratio ≥ 4 was associated with worse cancer-specific survival [13]. Outlining prognostic markers even in an aggressive disease like CDC could be useful to guide the clinician in choosing the best treatment option.

Although significant achievements have been reached in the clinical management of clear cell RCC with targeted therapy and immunotherapy, little progress has been shown in the treatment of CDC.

When metastatic, this disease has been usually treated as a urothelial tumor, with chemotherapy combinations regimens, usually cisplatin or carboplatin plus gemcitabine [14]. Results with these therapy schedules are poor, with survival rates of less than 12 months. There is less experience with other approaches, such as targeted therapy and immunotherapy, but the intrinsic aggressiveness of this disease seems overwhelming. In recent years various efforts have been carried out to molecularly characterize this rare tumor. High-throughput transcriptome analysis and next generation sequencing allowed a deep characterization of the biology of CDC, expanding the background for a targeted and biologically driven treatment approach in the next future.

CDC is an orphan disease with limited and unsatisfactory treatment options particularly when metastatic; according to international guidelines, enrollment in clinical trials is the preferred strategy for patients with this peculiar renal cancer subtype [15].

Here we review the up-to-date state of art regarding CDC, trying to identify future perspectives for alternative treatment strategies to solve this unmet clinical need.

Diagnostic presentation

CDC is more common in males with a 2:1 ratio, and in black than in white patients; the onset age range is reported between 13 and 83 years (mean age 55 years) [16,17]. Usually the patient presents with abdominal pain, gross hematuria, weight loss and flank mass. Patients may occasionally show positive urine cytology [1]. Collecting ducts carcinoma has an aggressive biologic behavior and in about one third of patients spread of disease can be observed as from diagnosis, affecting the prognosis [18]. Metastases at lungs, liver and adrenal glands are common; bony metastases are often osteoblastic, and lymph-node involvement is extremely frequent especially at cervical lymph nodes [19]. Of all renal cancers, CDC has the worst prognosis and approximately two third of patients die within 2 years from diagnosis [20].

The 3-year relative survival rates for localized, regional, and distant disease have been reported to be 93%, 45%, and 6%, respectively, although most patients present with T3 and T4 disease. Patients presenting with metastatic disease reach a median overall survival of only 11 months [21]. Early diagnosis is essential and may increase patient survival.

At CT scans CDC commonly appears as a mass in the renal medulla involving renal sinus, with infiltrative growth, preserved renal contour, cystic component and calcification foci, and weak and heterogeneous enhancement. Common findings include perinephric stranding and vascular invasion, while lymphadenopathy and distant metastasis are detectable in 56% and 33% of cases, respectively [22,23].

Macroscopically CDCs show a tan to white color with areas of hemorrhage and necrosis. The diameters range from 1 to 16 cm with irregular and infiltrative borders. CDCs can infiltrate the cortex and often extent beyond the kidney parenchyma including the perirenal fat, adrenal gland, and Gerota's fascia, with satellite nodules commonly detectable [24].

Microscopically CDCs display a tubular or tubule-papillary growth pattern where irregular angulated glands infiltrating renal parenchyma are associated with a desmoplastic stroma (Fig. 1A and B). Sarcomatoid or rhabdoid differentiation can be present and small vessels infiltration is commonly described, underlining the aggressiveness of this tumor. Tumor cells appear cuboidal, columnar, or hobnail with pale eosinophilic or clear cytoplasm and high-grade nuclei and prominent nucleoli with focal spindle cell differentiation (Fig. 1C). Cytoplasmic and luminal mucin is characteristic of this tumor, as mucin is not produced in renal cell carcinoma. Acute or chronic inflammatory cells infiltration in surrounding stroma is commonly observed [16,24–26].

Immuno-histochemistry (IHC) supports the diagnosis of CDC excluding other entities and avoiding misdiagnosis especially with the upper tract urothelial carcinoma (UTUC). Both neoplasms are highly infiltrating carcinomas with strong desmoplastic response in the medullary region, and they can show overlapping morphologic features. Foci of tubular structures can be found in UTUC samples, mimicking a CDC, while CDC can display occasional nested areas with urothelial-like morphology. CDCs usually express high molecular weight keratins such as 34bE12 and CK19 or CK7 commonly co-expressed with vimentin. Nuclear expression of PAX2 and PAX8 is present in the majority of CDC samples as well as Ulex europaeus lectins (Ulex-1) and peanut lectin agglutinin (PNA). To avoid misdiagnosis with urothelial carcinoma IHC for p63 and GATA3 is recommended and its positivity addresses the suspect toward this condition [24,27–30].

Biology

Due to the rarity of CDC, there is a lack of knowledge on the biology and molecular architecture of this tumor as compared to other RCC subtypes, whose genetics have been extensively analyzed and crucial proliferative and metabolic pathways have been identified.

Various cytogenetic studies have been conducted and different chromosomal aberrations have been described. DNA losses are frequent with loss in the chromosome 1q, 6p, 8p, 9p and 21q as well as loss of Y [1,27,31,32]. The impact of such alterations on prognosis and response to treatment is unclear.

The only case series evaluating the presence of c-erbB-2 oncogene amplification have been published in 1997 by Selli et al. [33]. Human epidermal receptor-2 (HER2) amplification has been documented in about one third of transitional cell carcinomas of the bladder [34–36]. Based on the hypothesis that CDC and urothelial carcinomas share common biological characteristics Selli et al. investigated the presence of HER2 amplification by competitive PCR in 11 cases of CDC. The c-erbB-2 oncogene amplification was present in 5 out of 11 cases (45%) with a number of copies ranging from 4 to 12. All patients presenting this alteration died within one year, supporting the negative prognostic role of HER2 amplification.

With the evolution and widespread of the omics technologies, a scientific interest in the in-depth understanding the biology of this orphan disease is growing.

Pal et al. performed a comprehensive genomic profiling of 17 samples from locally advanced or metastatic CDC [37]. Multiple recurrent genomic alterations were detected, most commonly in *NF2* (29%), *SETD2* (24%), *SMARCB1* (18%), and *CDKN2A* (12%). In addition to five patients with *NF2* truncations, clinically relevant genomic alterations of *PIK3CA*, *PIK3R2*, *FBXW7*, *BAP1*, *DNMT3A*, *VHL*, and *HRAS* were also identified at a frequency of 6% each. *FH* homozygous loss was identified in two out of nine patients (22%). The authors highlight the relevance of these alterations on the basis of the following putative therapeutic strategies: (1) mTOR pathway inhibition (*VHL*, *NF2*, *PIK3CA*, and *PIK3R2*) [38–43]; (2) histone deacetylase inhibition (*FBXW7*) [44]; (3) EZH2 inhibition (*BAP1* and *SMARCB1*) [45]; (4) VEGF inhibition (*VHL*); (5) DNA methyltransferase inhibition (*DNMT3A*) [46]; (6) EGFR inhibitor resistance (*HRAS*) [47]; and (7) CDK4/6 inhibition (*CDKN2A*) [48].

The latter alteration has been extensively described by Wang et al. analyzing 7 samples of CDC [49]. The authors performed whole exome sequencing and transcriptome sequencing on 7 CDC samples and 4 samples with matched non-tumor tissue. The major finding of this analysis was the detection of *CDKN2A* homozygous deletion in 3

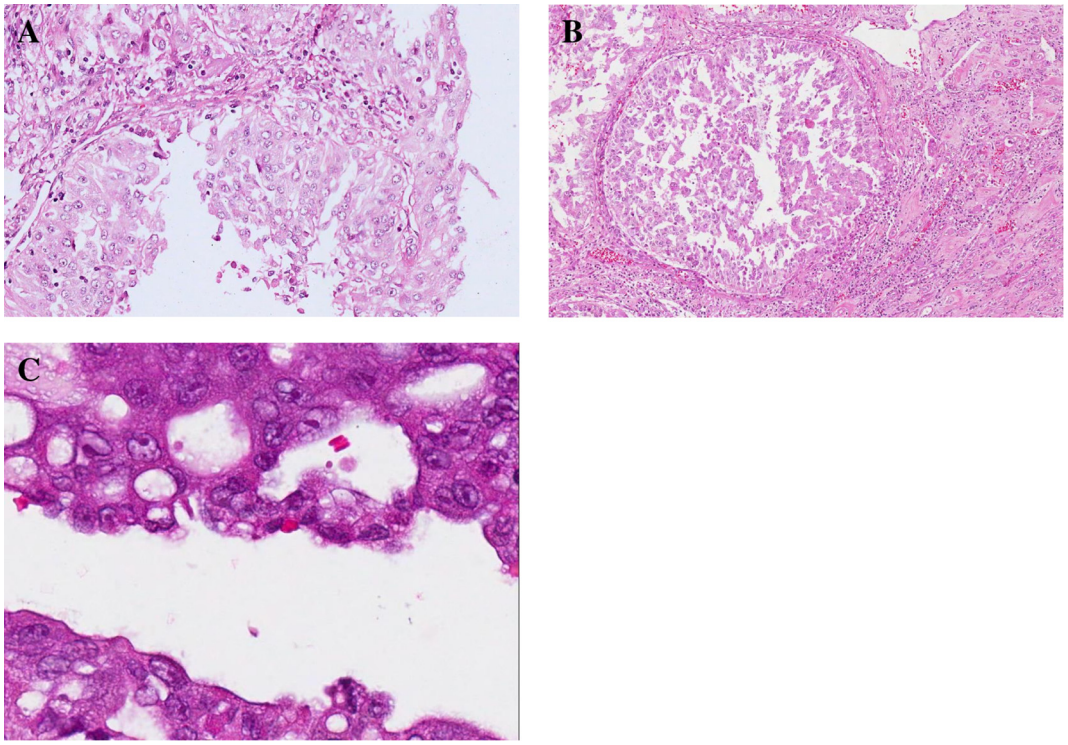

Fig. 1. A and B Microscopically CDCs display a tubular or tubule-papillary growth pattern where irregular angulated glands infiltrating renal parenchyma are associated with a desmoplastic stroma. C, By definition, these tumor cells almost always display high-grade nuclear features.

samples and a non-sense mutation of the *CDKN2A*. To estimate the recurrent rate of *CDKN2A* abnormalities, Wang et al. performed FISH screening of additional 16 samples confirming the frequent loss (62.5%) of *CDKN2A* expression.

To assess the differences between CDC and UTUC, Malouf et al. performed RNA sequencing of 11 CDC together with 3 normal kidney tissue samples and 9 UTUC samples. They compared RNA expression profiles of the over mentioned samples with those of kidney cancers of diverse histology (clear-cell RCC, papillary RCC, translocation RCC) and bladder carcinoma by means of unsupervised hierarchical clustering. Interestingly they found that UTUC cases clustered with bladder carcinomas while CDC clustered with other RCC subtypes but within a distinct cluster. When focusing on genes up- and down-regulated in CDC samples compared to normal kidney tissue, the authors found an impairment in oxidoreductase activity, pyruvate metabolism, tricarboxylic acids cycle and aerobic respiration, with a significant down-regulation of *AMPK* gene, highlighting a metabolic shift in CDC. Twelve CDC samples were available to characterize tumor infiltrating lymphocytes (TILs). Of note, median CD8 TIL percentage was 11% (range: 0–25%), with a trend toward a higher percentage in metastatic versus non-metastatic tumors [50].

Choueiri et al. explored the programmed death-ligand 1 (PD-L1) expression by immunohistochemistry in both tumor cell membrane and tumor-infiltrating mononuclear cells (TIMC) of 101 samples of non-clear cell RCC [51]. Interestingly the authors found that 1/5 CDC samples was positive for PD-L1 expression in tumor cells while 5/5 CDC samples were positive for PD-L1 expression when considering the TIMC. PD-L1 positivity in tumor cells was associated with higher tumor grade and stage, as well as shorter overall survival (OS), while the association between PD-L1 expression in TIMC and survival showed only a trend to worse OS.

These findings could reshape the current unsatisfactory treatment armamentarium for this particularly rare and aggressive disease.

Current treatment options

Overview of localized CDC

As previously reported, CDC is rarely diagnosed as a localized disease. In this scenario surgery is the only potential curative treatment with long-term survival patients depicted as case reports [52,53]. The role of adjuvant or neoadjuvant therapies is not known.

Metastatic CDC

Surgery

Cytoreductive nephrectomy is performed routinely, leading to a diagnosis of CDC only after the primary surgery of which the role in this scenario is lacking in the literature. Méjean et al. reported a median survival of only 6 months for 10 CDC patients (of whom 7 with metastatic disease at presentation) that received nephrectomy. 3 patients died during the perioperative or postoperative period [54]. On the contrary, an analysis on 227 cases of CDC from the SEER database examined by Abern and colleagues, revealed that patients selected for cytoreductive surgery had improved survival. However, the lack of data regarding baseline characteristics of the patients and further treatment administered, cannot exclude a surgery selection bias of these patients [55].

Patients with CDC usually have a poor performance status at diagnosis. Considering the invasive nature of CDC, the biological aggressiveness of this tumor, surgical complications and recovery may prevent a patient from receiving systemic therapy, suggesting a CDC diagnosis by biopsy the best practice to pursue.

Radiotherapy

Radiotherapy by means of palliative external beam therapy could be an effective symptoms-relieving treatment [56]. Common symptomatic lesions such as bone metastasis should be periodically evaluated to promptly address the patient to a radiotherapist.

Table 1
Completed and ongoing clinical trials evaluating treatment regimens for mCDC patients. ORR: objective response rate; PFS: progression free survival; PI: principal investigator; DR: drug-related; AEs: adverse events.

	Phase	Treatment regimen	Line of treatment	Patients (n)	Primary objective	Results
Chemotherapy:						
Oudard et al. (2007)	II	gemcitabine plus cisplatin or carboplatin	I	23	ORR	26%
Sheng et al. (2018)	II	sorafenib plus gemcitabine and cisplatin	I	26	PFS	8.8 months
Thibault (PI) (ongoing) NCT02363751	II	bevacizumab plus gemcitabine and platinum salts	I	enrolling (41 estimated)	ORR, 6-months PFS	–
Targeted therapy						
Procopio (PI) (ongoing) NCT03354884	II	cabozantinib	I	enrolling (23 estimated)	ORR	–
Immune-checkpoint inhibitors:						
Sternberg et al. (2019)	IIb	atezolizumab	II or further	1004 [§] (8 CDC)	Safety	13% Grade ≥ 3 DR AEs
Marabelle (PI) (ongoing) NCT03012581	II	nivolumab	II or further	enrolling (300 estimated) [*]	ORR	–

[*] Six cohorts including one for non-clear cell renal cell carcinoma.
[§] The trial allowed the inclusion of patients with urothelial or non-urothelial carcinoma of the urinary tract.

Systemic treatments

Due to the rarity of CDC, evidences from randomized clinical trials evaluating the best treatment for patients with mCDC are lacking. Completed and ongoing prospective single-arm clinical trials evaluating treatment regimens for mCDC patients are depicted in Table 1.

1) Chemotherapy:

Previous reports illustrate the role of chemotherapy for the treatment of metastatic CDC (mCDC) with agents effective in urothelial carcinoma. Isolated experiences and case reports observed limited responses to MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) [57,58] paclitaxel [59], paclitaxel and carboplatin [60,61], doxorubicine and gemcitabine [62]. Peyromaure et al. treated two patients with CDC and synchronous metastasis with cisplatin plus gemcitabine as first-line therapy. Each patient achieved an objective response after 3 chemotherapy cycles and remained disease-free 27 and 9 months after nephrectomy, respectively [60,62,63]. On this basis, Oudard et al. designed a prospective phase II trial to evaluate the activity of the standard chemotherapy regimen defined by a gemcitabine and platinum salts combination in patients with previously untreated mCDC [14].

23 patients with mCDC were treated with gemcitabine and cisplatin or carboplatin for six cycles. Median patient age was 65 years, and 87% had previously undergone nephrectomy. In 96% of the patients, Eastern Cooperative Oncology Group performance status was 2 or less. Objective response rate (ORR) reached with this regimen was 26%, median progression-free (PFS) and OS was 7.1 and 10.5 months, respectively. Toxicity was mainly hematological with grade 3–4 neutropenia and thrombocytopenia in 52% and 43% of patients, respectively.

Recent results from a prospective phase II trial conducted in China that enrolled 26 mCDC patients to receive a first-line treatment with sorafenib plus gemcitabine and cisplatin showed a median PFS and OS of 8.8 and 12.5 months, respectively. The ORR with this regimen was 30.8%. Serious grade 3–4 toxicities included leucopenia (26.9%), thrombocytopenia (23.1%), anemia (11.5%) and palmar-plantar erythrodysesthesia (7.7%) [64].

Pécuchet et al. investigated the role of a triplet containing bevacizumab, gemcitabine and platinum salt, in five patients with previously untreated mCDC. There were three cases of partial response (PR), one case of stable disease (SD) and one case of complete remission (CR) after surgery of the only metastatic site [65]. These results led to design the current ongoing phase II trial conducted in France. Investigators estimated to enroll 41 patients with mCDC receiving the previously adopted treatment regimen. The two co-primary endpoints of the study are objective response rate (CR or PR) and PFS rate at six months [66].

2) Targeted therapy:

Tyrosine kinase inhibitors (TKI) directed against the vascular endothelial growth factor (VEGF) pathway and inhibitors of the mammalian target of rapamycin (mTOR) are milestone strategies for the treatment of metastatic clear cell RCC. Less stronger evidences are available on the efficacy of such agents for the treatment of non-clear cell RCC, and, particularly for mCDC, neither prospective clinical trials have been conducted, nor mCDC patients were included in clinical trials evaluating targeted therapies in non-clear cell RCC [67].

A small retrospective analysis of 13 mCDC patients evaluated the activity of different TKIs: sunitinib, sorafenib, pazopanib and the mTOR inhibitor temsirolimus. Only two patients were able to receive a second line of treatment with sunitinib after disease progression. No patients were alive at five years. Five patients developed early progression of disease with an OS of 4 months, while two patients had a long-lasting disease control with an OS of 49 and 19 months, respectively [68]. Yin

et al. reported a case of mCDC patient diagnosed with nephrectomy, that locally progressed after two lines of chemotherapy, and then received chemoradiation with carboplatin and paclitaxel with disease response. Thanks to a genomic profiling, a single genetic change in the *NF2* gene was detected. As previously described mutations in *NF2* is recurrent in CDC samples [37], and preclinical studies showed that *NF2* impaired human cancer cells exhibited rapamycin-sensitive constitutive mTOR complex 1 activation [43]. Drawing from these considerations, the mTOR inhibitor everolimus was rationally selected for this patient with a successful disease stabilization lasting 9 months [69].

Other smaller experiences have been reported in the literature: Miyake et al. [70] and Chua et al. [71] presented case reports of partial response of metastatic CDC after sunitinib therapy. Ansari et al. documented a response, with minimal side effects, to sorafenib in a patient with metastatic CDC [72]. The same TKI was administered at a patient with pre-treated mCDC achieving a partial response and a PFS lasting for 12 months [73], while Mennitto et al. reported an encouraging result in a patient treated with cabozantinib [56].

The only prospective phase II trial evaluating the activity and safety of the targeted agent cabozantinib as first-line treatment for mCDC patients is current ongoing at Fondazione Istituto Nazionale dei Tumori in Milan [74]. The study design is based on a Simon's two stage optimal design: to complete the first step at least 2 responses in 9 patients were needed. This encouraging result has been achieved with two PR and two SD reported as best response. Treatment was feasible and well tolerated with no G3-G4 adverse events. The enrollment is ongoing to reach the preplanned goal of 23 patients.

Exploiting new treatment strategies: Case reports

As previously remarked, evidence-based data from clinical trial evaluating the best treatment for mCDC patients are poor and are summarized in Table 1. Due to the rarity of this disease, experiences derived from case reports gain significance, especially if the proposed treatment approach is biologically driven.

Bronchud et al. described a mCDC patient with high disease burden at diagnosis: both lungs, pelvic bones, axial skeleton, and the central nervous system. His performance status was poor with an ECOG (Eastern Cooperative Oncology Group) grade of 3. Thanks to a deep characterization of the primary tumor from the diagnostic biopsy the authors found HER2 overexpression detected by fluorescence in situ hybridization and immunohistochemistry. The patient received oral capecitabine together with double HER2 blockade with both intravenous trastuzumab and oral lapatinib. The treatment was well tolerated with only mild fatigue and diarrhea; both clinical and radiological responses were reported [75].

Three case reports described the safety and activity of the immune-checkpoint inhibitor nivolumab, a monoclonal antibody directed against the programmed cell death protein 1 (PD-1), in patients with mCDC pre-treated with chemo and targeted therapy [76–78]. On the contrary previous reports with immunotherapy by means of INF-α or IL-2 for patients with CDC showed negative results [10,11,79]. The authors of the first two cases found PD-L1 overexpression by immunohistochemistry in the tumor tissue samples, while the PD-L1 status in the latter was not available. As previously reported [51], the high expression of PD-L1 in non-clear cell renal carcinoma, including CDC, correlates with a poor prognosis, that could be reversed if an immune-checkpoint inhibitors approach will be validated in these rarer histological subtypes of cancer.

Koshkin et al. evaluated the clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma including 4 patients with mCDC, of whom one experienced a partial response [80].

To our knowledge there are no immunotherapy trials ongoing specifically for CDC, however clinical study that allowed enrolment of CDC patients have been carried out. Recently primary results from a phase IIIb study that enrolled 1004 patients with locally advanced or metastatic pre-treated urothelial or non-urothelial carcinoma of the urinary tract, including 8 CDC patients, to receive atezolizumab (a monoclonal antibody directed against PD-L1), have been published. Primary endpoint was safety with 8% of patients that discontinued because of toxicity and 13% of Grade ≥ 3 adverse events treatment-related. Overall outcomes results were median OS of 8.7 months (95% CI 7.8–9.9), median PFS of 2.2 months (95% CI 2.1–2.4), and ORR of 13% (95% CI 11–16%; 3% complete responses) [81]. Unfortunately, no data regarding the outcome of the eight CDC patients treated are available. Moreover, a multicentric phase II trial with nivolumab for pre-treated rare tumors, with a cohort for non-clear cell RCC that includes CDC is currently ongoing in France [82]. These experiences on the effectiveness of immunotherapy in mCDC guided by a biological rationale could reshape the treatment armamentarium of this aggressive and treatment-orphan disease.

Conclusions

Despite clinical advances in the treatment of metastatic renal cell carcinoma, the prognosis of patients with mCDC remains poor. Current available treatment options are unsatisfactory and results from prospective trials are limited. Surgery by means of nephrectomy is the only potentially curable option in patients with limited disease, while doublet chemotherapy regimens containing platinum salts and gemcitabine are advised for patients with mCDC. The in-depth understanding the biology of this peculiar renal cancer subtype has led to the growth of available data concerning potential predictive biomarkers. This approach will play a key role to find new and effective treatment strategies in the next future. Referring the patient to a specialized center to molecularly characterize the disease and evaluate enrollment in available clinical trials is the preferred strategy. To best address this purpose, international collaborations are encouraged to design prospective trials evaluating experimental treatments in patients with collecting duct histology.

Declaration of Competing Interest

Giuseppe Procopio declares advisory/consultant role for the following organizations from whom received honoraria: Bayer, BMS, Ipsen, Janssen, Merk, MSD, Novartis, Pfizer. Elena Verzoni declares advisory/consultant role for the following organizations from whom received honoraria: Bayer, BMS, Ipsen, Janssen, Merk, MSD, Novartis, Pfizer. Filippo de Braud provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom received honoraria or education grants: Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, Eli Lilly, F. Hoffmann-La Roche, Ignyta, MSD, Merck Serono, Novartis, Pfizer. Filippo Pagani, Maurizio Colecchia, Pierangela Sepe, Giulia Apollonio and Melanie Claps declare no conflicts of interest.

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