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# CARCINOMA OF THE COLLECTING DUCTS OF BELLINI OF THE KIDNEY: ADJUVANT CHEMOTHERAPY FOLLOWED BY MULTIKINASE-INHIBITION WITH SUNITINIB

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**Abstract**
*Introduction:* Carcinoma of the collecting ducts of Bellini of the kidney (CDC) is very rare but among the most aggressive urological entities. Standard therapy is not well defined with questionable efficacy.
*Methods:* We present two cases of male patients (49 and 66 years old) with pT3a pN2 CDC treated with a combination of cisplatin plus gemcitabine in an adjuvant setting. Following recurrence the multi-kinase inhibitor sunitinib was administered.
*Results:* Radical nephrectomy with lymphadenectomy revealed CDC in stage pT3a pN2 M0 G3 R0 in both patients. 4 courses of adjuvant chemotherapy with cisplatin 70mg/m² and gemcitabine 1500mg/m² were given. Side effects according to the NCI 3.0 common toxicity criteria were limited to grade 2 asthenia and grade 2 thrombozytopenia/leucopenia. Restaging revealed local recurrence and lymph node metastases. Both patients were re-operated and metastatic CDC was found. Second line therapy with sunitinb malatat (Sutent®, Pfizer Inc. U.S.) at 50mg p.o. was given. Grade 3 leucopenia and thrombocytopenia and grade 2 asthenia and mucositis were not dose-limiting. After two cycles multiple liver, lung and bone metastases and mediastinal lymphopathy occured. 8 weeks later the patients died with a survival of 8 months from initial diagnosis.
*Conclusions:* Adjuvant gemcitabine plus cisplatin did not delay recurrence of CDC after surgery. Metastasectomy either had no influence on the course of disease. Anti-angiogenetic therapy with sunitinib treatment was not effective, possibly related to a low vascular density (CD31 expression) in CDC.

*Key words:* renal cell cancer; tyrosin kinase inhibitor; sunitinib; collecting duct carcinoma

## INTRODUCTION

Carcinoma of the collecting ducts of Bellini of the kidney (CDC) is a rare and extremely aggressive entity of renal cell cancer (RCC). CDC accounts for approximately 1-1.5% of RCC. Predominantly it occurs in younger male patients (median age at diagnosis 43 years, male to female ratio 2 : 1) [1-5]. Clinical presentation is not different from other renal cancers with almost 40% of the patients presenting without any symptoms and incidental tumours. The classical triad of the symptoms, flank pain, palpable tumour and gros hematuria are mostly associated with higher tumour stages and mainly metastatic disease. The majority of patients with CDC do have metastatic disease at presentation with regional, supraclavicular or cervical lymph nodes being the most frequent metastatic site [1, 2, 4, 5]. Most CDC are medullary located with frequently cystic components. The renal contour is preserved in the majority of cases and the contrast enhancement in computed tomography (CT) is weak and heterogeneous [6]. Unfortunately these CT findings are non-specific and do not allow differentiation from other subtypes of RCC. Thus CDC needs to be treated like all other RCC and surgery has to be the primary choice of treatment.

## HISTOPATHOLOGY

CDC is a very rare and often difficult histological diagnosis. Small tumours demonstrate with central, medullary location their histogenetic development from the collecting ducts of Bellini. Most tumours are large with a typical multinodular, permeative infiltration of the kidney, often sparing glomerula, with ill-defined margins and frequent infiltration into perinephric tissues und nodal and hematogenous metastases (Fig. 1). A tubular or tubulopapillary growth pattern predominates with high grade cellular atypia. Positive staining for low and high weight cytokeratins, CD15, epithelial membrane antigen, Ulex europaeus agglutinin-1, Fez1 and peanut lectin and negative staining for CD10 supports CDC in distinction from other types of RCC or from metastatic disease. In comparison to conventional (clear cell) RCC staining with CD31 identifies a striking paucity of intratumoral blood vessels (Fig. 2); [7-11].

## THERAPEUTIC APPROACHES

So far no standard therapy exists for CDC. Although immunotherapy based on interleukin-2 and interferon alpha has shown efficacy in some cases it does not ap-

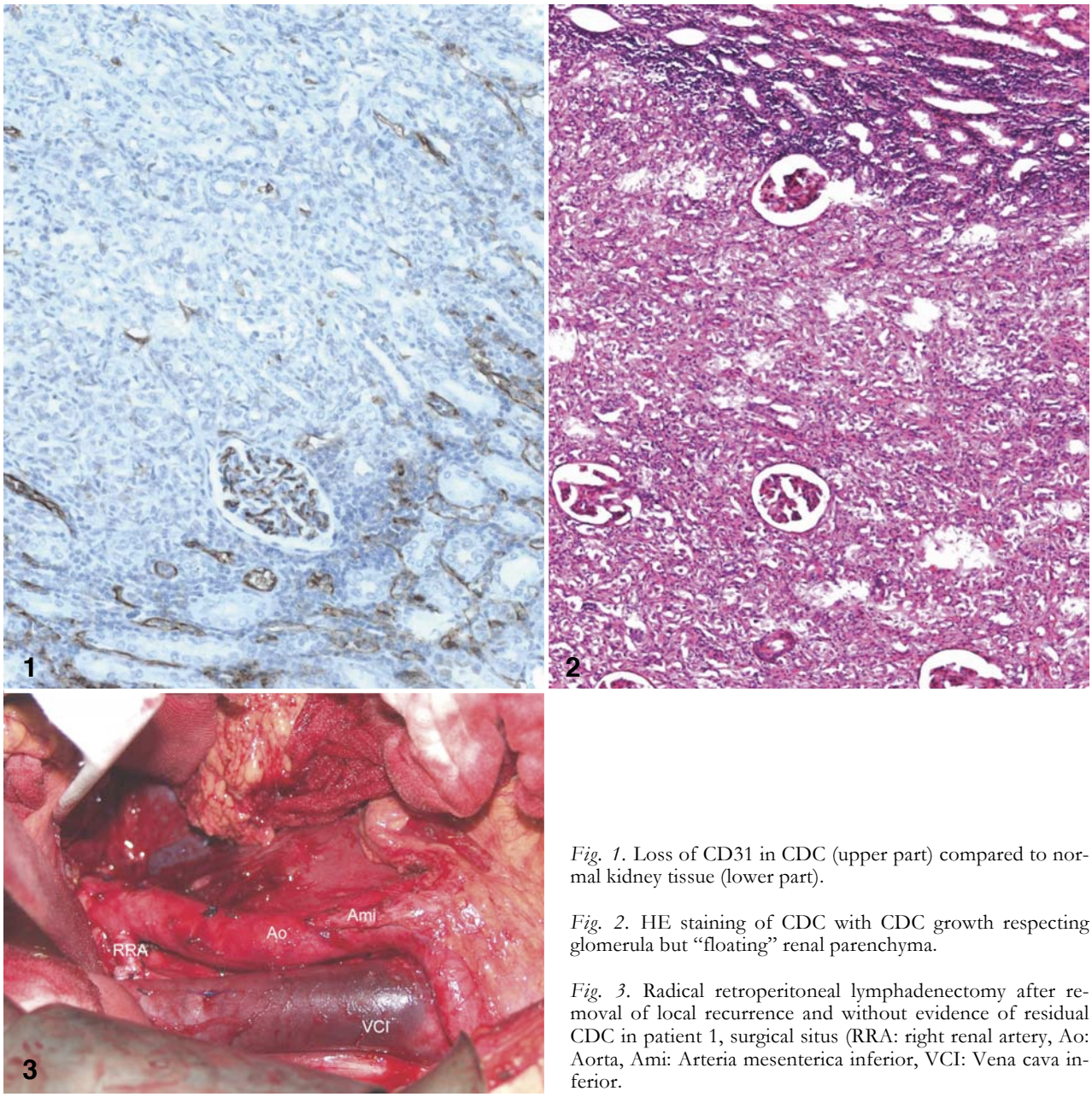


*Fig. 1.* Loss of CD31 in CDC (upper part) compared to normal kidney tissue (lower part).

*Fig. 2.* HE staining of CDC with CDC growth respecting glomerula but "floating" renal parenchyma.

*Fig. 3.* Radical retroperitoneal lymphadenectomy after removal of local recurrence and without evidence of residual CDC in patient 1, surgical situs (RRA: right renal artery, Ao: Aorta, Ami: Arteria mesenterica inferior, VCI: Vena cava inferior.

pear to be beneficial in all patients [12-14]. While there are rationales to treat CDC more like transcitional cell cancer (TCC) of the kidney no prospective data can be found in the literature [2]. There are some cases of CDC treated with gemcitabine and cisplatin in second line indication with achieved stabilisation or partial remission and beneficial palliation [1, 12, 13]. Thus this regimen was proposed as quasi-standard treatment option for CDC. The combination of paclitaxel plus carboplatin had similar effects in one case [15].

## Methods

Two asymptomatic patients were admitted due to an incidental tumour of the kidney seen in echography. Both were male patients, one was 49 years old the other one 66 years. We present prospective data on two patients that were treated with adjuvant gemcitabine in combination with cisplatin after radical nephrectomy for CDC. Following recurrence and repeated surgical intervention sunitinib was administered orally.

## Results

Preoperative computed tomography (CT) revelead in both cases an organ confined cT2 situation with all criteria of malignancy being fulfilled. In one patient the left sided tumour had a size of 4 cm in diameter with the margin being not very well restricted. In the other patient the situation was equal with a the right sided tumour of 6 cm also not having very well defined boundaries (Fig. 4). Staging including skeletal scintygraphy and whole-body CT revealed no further metastatic lesions or suspect lymph nodes.

Both patients received radical nephrectomy and extended lymphadenectomy from a flank incision. Histology proved collecting duct (Bellini) carcinoma (CDC) in both patients in stage pT3a pN2 G3 R0 M0.

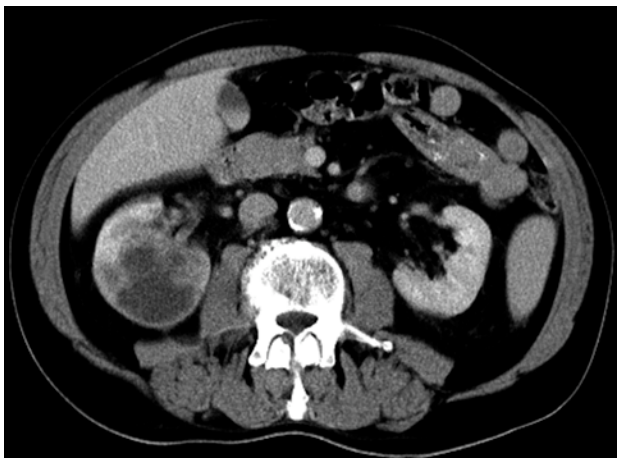

*Fig. 4*. Computed tomography of the abdomen showing a 6cm unregular mass of the right kidney, resembling CDC.

Based on similarities of CDC and TCC and encouraging literature reports [2, 12, 13, 16] patients were treated with an adjuvant regimen consisting of gemcitabine 1,250mg/m² on days 1 and 8 and 70mg/m² cisplatin on day 1 for 2 cycles. Side effects were rated according to the NCI 3.0 common toxicity criteria. Major toxicity consisted of grade III thrombopenia and neutropenia as well as grade II vomiting and nausea in both cases. Dosage was not reduced.

After 2 cycles a repeated CT of thorax and abdomen was performed revealing local recurrences in both cases. Both patients were treated by radical retroperitoneal lymphadenectomy and removal of the recurrent mass as demonstrated in Figure 3. Histology showed metastatic lymph node lesions of CDC without positive surgical margins.

Second line therapy with sunitinib malatat (Sutent®, Pfizer Inc. U.S.) at a dose of 50mg orally for 4 weeks followed by a 2 weeks wash out phase was started 4 weeks after surgery.

In contrast to our RCC patients sunitinib therapy was clinically hardly tolerated. Major side effects were grade II fatigue, neutropenia and vomiting, as well as stomatitis and mucositis. Both patients reported erectile dysfunction. No dose reduction was needed.

Restaging was performed after two cycles with a CT of thorax and abdomen revealing metastatic disease with disseminated liver and bone metastases in both cases and multiple lung metastases in one case. Therefore sunitinib was stopped and palliative treatment was given. Both patients died 8 months after initial diagnosis.

## Discussion

So far no standard therapy exists for CDC. Although immunotherapy based on interleukin-2 and interferon alpha has shown efficacy in some cases, it does not appear to be beneficial in all patients [12-14]. While there are rationales to treat CDC more like transcitional cell cancer (TCC) of the kidney no prospective data can be found in the literature [2]. There are some cases of CDC treated with gemcitabine and cisplatin in second line indication with achieved stabilisation or partial remission and beneficial palliation [1, 12, 13]. Thus this regimen was proposed as quasi-standard treatment option for CDC. The combination of paclitaxel plus carboplatin had similar effects in one case [15].

A matched analysis of CDC with RCC of the same stage showed no difference in cancer-specific mortality between the two groups. Both groups were matches according to Fuhrman grade, symptom classification and TNM stage as well as tumour size within 1cm. One and five years survival rates for CDC were 86 and 48% compared to 86% and 57% in RCC. The slightly better 5year survival rate of RCC might contribute to the fact that systemic treatment in RCC is more effective than in CDC. Nonetheless CDC patients more often present with advanced stage and more aggressive disease than RCC patients and long term survival seems to be restricted to stage I tumours [17, 18]. This retrospective analysis is limited due to the fact that tumours with a differing in size of up to 1cm may behave completely different. But the greatest limitation of this analysis seems to be that no central pathological re-evaluation was performed. As pathological diagnosis of CDC is difficult one might estimate that some specimens might not match exactly the immunohistochemical criteria related to the diagnosis of CDC. Similarities to TCC might lead to a misinterpretation with consequence to prognosis. Also no information was available on systemic treatment of the inhomogeneous group treated at different institutions. In contrast Tokuda et al. reported on the largest series of CDC in Japan. Of 120 initially diagnosed CDC cases central pathological re-evaluation ruled out 39 cases. These ruled out cases that had been initially identified as CDC were papillary RCC, TCC chromophobe RCC, oncocytoma and a fibroepithelial polyp. In patients with confirmed CDC 1, 3, 5 and 10-year disease specific survival was 69.0%, 45.3%, 34.3% and 13.7%, respectively. Systemic therapy consisted of mainly immunotherapy followed by chemotherapy and radiation as well as metastasectomy. Unfortunately no information is given on the results of these treatment modalities.

The largest single centre series of systemic treatment reported to date is a retrospective review of 12 patients of the M.D. Anderson cancer centre published in 1993 and a retrospective study by Vecchione et al. of 11 patients [10, 19]. In these series the median survival was 22 and 12 months respectively (range 2-65 months) with a tendency of higher stages and metastatic disease being related to a shorter survival time. While in the M.D. Anderson series long lasting response was achieved in 7 patients with regiments that were based upon interferon alpha s.c. with our without combination of interleukin-2 s.c. and no effect of the classic MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) scheme was reported Gollob et al. reported a long-term remission for 20 months achieved with neo-adjuvant paclitaxel plus carboplatin and consecutive nephrectomy after partial remission [15]. But in this case the initial diagnosis of CDC and the histological review of the primary tumour were different. The authors interpreted this as a selection effect of chemotherapy but no further information on immunohistochemical quality of the tissue was given.

*Table 1.* Therapeutic regimes in CDC.

| | N | Therapy | Response (Duration) | Survival months (range) |
|---|---|---|---|---|
| Dimopoulus, 1993 [19] | 6 | IFN + IL2 | 2 SD (10; 15 mo) 1 NED(30mo). | } median 22 (4-65) |
| Dimopoulus, 1993 [19] | 7 | MVAC | 1 MR (5mo) | |
| Dimopoulus, 1993 [19] | 1 | IFN + 5-FU +Mitomycin-C | 1 SD (16mo) | |
| Kirkali, 1996 [20] | 1 | IFN | 1 NED (19mo) | |
| Gollob, 2001 [15] | 1 | paclitaxel + carboplatin neoadjuvant + nephrectomy | 1 NED (20mo) | |
| Milowsky, 2002 [16] | 1 | paclitaxel + ifosfamide + cisplatin | 1 PR (2 mo) | 10 |
| Mejean, 2003 [21] | 10 | surgery alone | 2 NED (99; 100mo) | median 9 (3-100) |
| Peyromaure, 2003 [13] | 2 | gemcitabine + cisplatin | 2 CR (27; 9 mo) | |
| Peyromaure, 2003 [13] | 1 | prednisolone | PD | 5 |
| Peyromaure, 2003 [13] | 1 | IFN | 1 PR (6 mo) | 24 |
| Fakhrai, 2005 [12] | 1 | Gemcitabine + cisplatin | 1 PR | |
| This series | 2 | Gemcitabine + cisplatin followed by sunitinib | 2 PD | 8 |

IFN: interferon alpha; IL2: interleukin-2; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; 5-FU: 5-flurouracil, MMC: mitomycin-C; SD: stable disease; NED: no evidence of disease; MR: minor response; PR: partial response; CR: complete response; PD: progressive disease

Results of different therapeutic approaches are listed in Table 1.

Our patients were treated with an adjuvant chemotherapy resembling standard chemotherapy for TCC. In the initial situation no evidence of disease after complete surgical removal was evident. The decision to give adjuvant therapy was based upon the latest reports from Gollob and Fakhrai that proofed efficacy of TCC-chemotherapy with CDC [12, 15]. Unfortunately we could not see the same effects as in the literature. The first restaging revealed recurrent disease in both patients. As we saw only locally recurrent disease without systemic spread we decided to treat the situation surgically again, which is according to our protocol in local recurrence of RCC.

An explanation for ineffectiveness of the chemotherapy could be that no kind of immuno-induction with e.g. IFN or IL-2 prior to this treatment was given. Most of the patients in literature receiving chemotherapy had some form of first-line immunotherapy. Alternatively this form of CDC in our patients was resistant to gemcitabine plus cisplatin.

As both patients had a strong attitude against immunotherapy and we decided prior to treating the patients to switch to a multi-tyrosinkinase-inhibitor, sunitinib was started. Again at the beginning of this treatment no evidence of disease was found. Another 10 weeks later disseminated metastatic disease was found under full-dose therapy. One explanation for this could be the low density of blood vessels (a lack of hypervascularisation) in CDC (see Fig. 2), (as documented by a low CD31 expression in the tumours). In contrast to RCC, sunitinib could eventually not inhibit the intracellular pathways of proliferation, thus rendering this approach ineffective as extra- and intracellular targets were not addressed.

According to these results one might estimate that immunotherapy could be valuable in first-line CDC treatment and that other agents should be given second line or in combination.

In conclusion adjuvant gemcitabine plus cisplatin could not delay recurrence of CDC after surgery. Metastasectomy either had no influence on the course of disease. Anti-angiogenetic therapy with sunitinib treatment was not effective, possibly related to the low density of blood vessels (a low CD31 expression) in CDC. Further treatment of CDC should stress immunotherapy based upon IL-2 or IFN. Further treatment should be evaluated in clinical multi-center trials and standardized histological characterisation of CDC should be performed to learn more about potential targets of antiangiogenetic drugs in CDC.

*Conflict of Interest Statements:* No conflict of Interest

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