HER2 Blockade in Metastatic Collecting Duct Carcinoma (CDC) of the Kidney: A Case Report

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Summary
Background: Collecting duct carcinoma of the kidney (CDC) is a rare cancer associated with bad prognosis and, at present, with no specific effective therapies. Case Report: We report a clinical case with disseminated high-grade CDC presenting with widespread metastasis to both lungs, pelvic bones, axial skeleton, and the central nervous system (posterior fossa, both hemispheres and pituitary-hypothalamic). The primary tumor in the kidney was demonstrated (by fluorescence in situ hybridization and immunohistochemistry with Herceptest (3+) score) to significantly overexpress HER2. Critically ill at presentation, the patient received oral capecitabine together with double HER2 blockade with both intravenous trastuzumab and oral lapatinib. His clinical response was a dramatic improvement and a progressive decline in the radiological size of all of his multiple cancer lesions. Conclusion: Double HER2 blockade is an effective therapy in disseminated CDC even in the presence of brain metastases.

Introduction
Collecting duct carcinoma (CDC) of the kidney, also known as Bellini’s tumor, is a rare type of renal cancer, accounting for some 1% of all renal malignancies. It is usually very aggressive and associated with bad prognosis. Despite several published accounts on response to chemotherapies and targeted therapies, no standard treatment exists and it could be considered as an orphan disease where specific targets for treatment are urgently needed [1–5]. The Heidelberg
On admission our patient was very distressed and breathless and reported to have lost some 10 kg in weight over a few weeks. He had significant polydypsia and polyuria, with blurred vision and increasing difficulties in standing up and moving about. His performance status was poor with an ECOG (Eastern Cooperative Oncology Group) grade of 3. His chest X-ray showed countless metastases in both lung fields (fig. 1), his bone scintigram confirmed multiple hotspots compatible with metastases in his right hip, pelvic bones and axial skeleton. Multiple brain metastases were detected by both computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain, with lesions in posterior fossa, both hemispheres and pituitary-hypothalamus, but no signs of midline displacement or hydrocephalus. A body CT scan showed a renal mass in his left kidney, measuring ~8 cm in diameter (fig. 2). An ultrasound guided biopsy was taken of this renal mass and histopathology was compatible with a high-grade CDC as confirmed by 2 independent expert histopathologists.

On the grounds of the clinical and radiological suspicion of diabetes insipidus, he was started on desmopressin. Because of a rapidly deteriorating general condition and uncontrolled symptoms, he received palliative radiotherapy to his right hip and started whole brain radiotherapy (30 Gy in 10 fractions plus 6 Gy boost over pituitary in 3 fractions) and concomitant systemic antitumor therapy with oral capecitabine (1,250 mg/m² every 12 h for 2 weeks out of every 3 weeks). After radiotherapy, a control MRI of the brain showed some disease progression and the patient continued therapy with capecitabine 3 times weekly (at the same dose) plus intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg intravenously every 3 weeks) plus oral lapatinib (750 mg/day to reduce risks of severe diarrhea) and intravenous zolendronic acid (4 mg). Treatment was very well tolerated and the patient’s symptoms (shortness of breath, extreme fatigue, pain, excessive thirst, and blurred vision) rapidly improved so that after only the second course of this therapy the patient was already up and about the ward. The patient remains alive and well at his home, 7 months after initiation of therapy, with an ECOG performance status of 1. His primary tumor in the kidney and most metastatic sites (figs. 3 and 4) continue to shrink to this date. He is tolerating treatment extremely well, except for some mild intermittent diarrhea and fatigue.
Discussion

In recent years several small studies or single case reports have suggested a variable degree of tumor responses to targeted therapies, including sorafenib, sunitinib and temsirolimus [11–13], most of them only partial and short-lived. In a recent Spanish series of 6 patients, none of these treatments appeared to be effective [14], and the median survival was only 5.5 months with only 2 patients, both with localized disease at diagnosis, surviving for longer than 1 year. In a retrospective analysis of 7 cases [5], 4 patients received first-line treatment with sorafenib, 1 with sunitinib and 2 with temsirolimus, and following progression 2 patients received second-line treatment with sunitinib. Unfortunately, 5 of these 7 patients developed early progression of disease, surviving only 4 months, and only 2 survived for more than 1 year. The authors concluded that further studies including biomarkers as predictive factors of tumor biology and clinical features are required to improve the management of this challenging disease [5].

To our knowledge, the only ‘druggable’ molecular target identified so far in a small Italian retrospective evaluation is HER2 oncogene, whose amplification, as detected by competitive PCR [15], was clearly related to poorer prognosis. In this small retrospective study, dating back to 1997, 11 CDC cases were studied by PCR, and HER2 oncogene amplification was present in 5 out of 11 cases (45%) with the number of copies ranging from 4 to 12. All patients presenting amplification of this oncogene died within 1 year (between 4 and 12 months) after surgery, while of the 6 patients without amplification at least 50% survived for longer than 3 years, suggesting that HER2 overexpression might indeed be relevant to prognosis and clinical behavior, and perhaps the tumor biology itself. No other specific molecular markers have yet been reported.

Several recent reports have indicated the clinical benefit of double HER2 blockade in breast cancer [16–18] and of oral lapatinib in the treatment of brain metastases in breast cancer patients [19, 20]. The rationale is the synergistic activity of double HER2 blockade on overexpressing tumor cells, and that lapatinib, being a small molecular weight oral tyrosine kinase inhibitor, should be capable of better penetrating the blood-brain barrier than trastuzumab, particularly in the context of brain metastases after brain radiotherapy. The triple combination of oral capecitabine, intravenous trastuzumab and oral lapatinib was very well tolerated by our patient and is probably quite suitable to patients with bad performance status. Dual inhibition of HER2 in breast cancer treatment has recently shown promise, and may well be also useful in other cancers overexpressing this receptor [21, 22].
To our knowledge the clinical case presented here is the first clinical report of safe and effective therapy in this rare form of cancer (CDC or Bellini’s tumor), based on a well-known cancer marker (HER2) and its overexpression. It seems highly unlikely that this very good systemic response in our patient was due to oral capecitabine alone, as brain metastases had actually increased in both number and size, following 1 course of oral capecitabine and concomitant whole brain radiotherapy. However, a synergistic effect of oral capecitabine with double HER2 blockade cannot be ruled out. Further studies are urgently warranted.

Disclosure Statement

The authors declare no conflicts of interest.

References