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Original Research

Sorafenib in combination with gemcitabine plus cisplatin chemotherapy in metastatic renal collecting duct carcinoma: A prospective, multicentre, single-arm, phase 2 study

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Abstract ***Background:*** Collecting duct carcinoma (CDC) is a rare type of renal cancer with a poor prognosis. As there are no standard guidelines for the management of metastatic CDC (mCDC), we evaluated the efficacy and safety of combined therapies of sorafenib, gemcitabine, plus cisplatin in patients with mCDC.
Materials and methods: A prospective, multicentre, single-arm, open-label, phase 2 trial (ClinicalTrials.gov identifier NCT01762150) that enrolled 26 mCDC patients with no prior systemic chemotherapy. Patients were treated with sorafenib (400 mg orally, twice daily) combined with chemotherapy (gemcitabine 1000 mg/m^2, intravenously for 30–60 min on days 1 and 8, plus cisplatin 25 mg/m^2, intravenously on days 1–3, repeated every 28 days for 4 cycles), until disease progression, unacceptable toxicity, or study discontinuation for

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any other reason. The primary end-points were progression-free survival (PFS) and 6-month PFS rate.

Results: The 6-month PFS rate was 65%, and the median PFS was 8.8 months (95% confidence interval [CI]: 6.7–10.9) with a median overall survival of about 12.5 months (95% CI: 9.6–15.4). The objective response rate was 30.8%, and the disease control rate was 84.6%. The treatment was generally well tolerated. Major grade 3/4 toxicities included leucopenia (26.9%), thrombocytopenia (23.1%), anaemia (11.5%) and palmar-plantar erythrodysesthesia (7.7%).

Conclusions: Though the combination of sorafenib and chemotherapy demonstrated a similar outcome as that of the previously reported regimens in patients with mCDC, this combination may be a suitable option for patients who have low Eastern Cooperative Oncology Group performance status or less metastatic sites.

1. Introduction

Collecting duct carcinoma (CDC) is a rare type of renal cell carcinoma (RCC) accounting for less than 2% of all RCC cases [1]. CDC arises from the papillary duct of the kidney and is a highly aggressive tumour with a poor prognosis. Patients usually present with an advanced disease stage at diagnosis and have a high incidence of early mortality in which 60–70% of patients die within 1–3 years of primary diagnosis [1–4]. Although substantial improvement has been achieved in the clinical outcomes of clear cell RCC with molecular targeted therapy and immunotherapy, little progress has been shown in the treatment of CDC. Conventional chemotherapy is commonly offered to these patients because a phase 2 study showed a 26% response rate in metastatic CDC (mCDC) with the gemcitabine and cisplatin/carboplatin (GC) regimen [5]. However, CDC does not respond well to chemotherapy, and thus has been a major challenge in the treatment of CDC.

Multitargeted kinase inhibitors have substantially improved clinical outcomes in metastatic RCC, thereby paving the way for research in other aggressive types of RCCs including mCDC [6,7]. Limited number of reports are available that describe the clinical outcomes of mCDC with multitargeted kinase inhibitors such as sunitinib and sorafenib [8–10]. Sorafenib, a multikinase inhibitor inhibits cell proliferation and angiogenesis, has been shown to be well tolerated when administered alone or in combination with the GC regimen in advanced solid tumours [11–14]. The 2011 retrospective analysis conducted in our institution reported well-tolerated and modest antitumour activity of sorafenib/sunitinib in combination with gemcitabine-based chemotherapy for the treatment of mCDC [15]. Therefore, we conducted a multicentre phase 2 study to prospectively evaluate the efficacy and safety of sorafenib in combination with GC chemotherapy as the first-line treatment in patients with mCDC.

2. Materials and methods

2.1. Study design and population

This was an investigator-initiated, prospective, open-label, multicentre, non-randomised, phase 2 trial (ClinicalTrials.gov identifier NCT01762150). Patients aged $\geq$18 years with a confirmed pathological diagnosis of mCDC, Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0–1, adequate haematologic (neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l and haemoglobin $\geq$9 mg/dl), hepatic (bilirubin <1.5 times upper limit of normal [ULN]; alkaline phosphatase $< 2 \times$ ULN in patients without bone metastases and transaminases $\leq 2 \times$ ULN) and renal (estimated creatinine clearance $\geq$50 ml per minute per m^2 according to Cockcroft-Gault formula) parameters and a measurable lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 were included in the study.

The pathological diagnosis criteria for mCDC included medullary involvement, tubular or tubulopapillary or tubulocystic growth pattern, high-grade nuclear feature and an infiltrative tumour border with desmoplastic stromal reaction [4]. Immunohistochemical staining with biomarkers (PAX8, PAX2, RCC marker, CD10, p63, 34BE12 and GATA3) was performed to confirm the pathological diagnosis and to exclude mimics such as high-grade urothelial carcinoma and RCC. Patients with brain metastases, poorly controlled hypertension and cardiovascular diseases within 6 months before screening were excluded from the study. Patients who received prior systemic chemotherapy were also excluded from the study.

This study was approved by the institutional review board or hospital ethics committee at each participating centre and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical