Introduction

In adults, renal cell carcinoma (RCC) is the most common type of kidney cancer, responsible for 90–95% of cases and the predominant pathology is clear cell carcinoma [1]. About 25–30% of cases are metastatic at the time of diagnosis [2]. As RCC is highly resistant to chemotherapy, immunotherapeutic agents such as interleukin 2 and interferon alpha (IFN-α) were the only available first-line treatments of metastatic disease [3-6]. But response rates with these agents are low and associated with significant toxicity [7-9].

Targeted agents were introduced over past years because of better understanding of oncogenetic mechanisms in metastatic renal cell carcinoma (mRCC). These agents include tyrosine kinase inhibitors (TKIs) such as sorafenib, sunitinib, pazopanib and axitinib [10-13]. These TKIs targeted the vascular endothelial growth factors receptors (VEGFR) and platelet-derived growth factors receptors (PDGFR) [14, 15].

Tyrosine kinases receptors have an important role in pathogenesis of clear-cell RCC through inactivation of the von Hippel–Lindau (VHL) gene. Inactivation of this gene leads to overexpression of VEGFR and PDGFR resulting in persistent stimulation of the receptors that can promote tumour growth, angiogenesis and metastasis [16].

Sunitinib produced clinical activity in patients previously treated with immunotherapeutic agents in two uncontrolled studies with objective response rates higher...
than that obtained by using immunotherapeutic agents as first-line treatment of metastatic cases [17, 18].

This retrospective study aimed at evaluation of patients with mRCC treated with sunitinib as first-line treatment in two centres as regard clinico-pathological character, treatment outcome, and survival.

**Patients and methods**

Review of recorded data from patient’s files with mRCC attended to Oncology centre, Clinical Oncology and Nuclear Medicine department, Mansoura University hospital were analysed during the period from August 2008 to December 2014. Those patients were treated with sunitinib as first-line therapy.

The data included patients’ characteristics such as age, sex, ECOG performance status (ECOG PS), number and sites of metastasis, time from diagnosis to treatment and pathological type. Also, we reviewed the response to sunitinib therapy, its adverse events and progression-free survival (PFS).

Staging procedures included computerised tomography (CT) of chest, abdomen and pelvis. Magnetic resonance imaging (MRI) of the brain, renal biopsy and bone scan were done. Measurable disease was assessed through the Response Evaluation Criteria in Solid Tumours (RECIST) [19].

Sunitinib was administered at a once daily dose of 50 mg orally for four weeks followed by two weeks rest, then repeated as six-week cycles till progression of disease, occurrence of intolerable adverse events or death. PFS was calculated from the date of diagnosis to the date of disease progression.

Adverse events were graded according to the Common Terminology Criteria for adverse events of the National Cancer Institute, v3.0 [20].

**Statistical method:**

Data were collected and analysed using SPSS version 15.0 (Chicago, IL, USA). Data expressed as number and percentile. Kaplan–Meier was used for survival function (PFS).

**Results**

This retrospective study included 26 patients; their characteristics are shown in Table 1. Median age was 56 years with male predominance (76.9%) and 61.5% of patients were of ECOG PS 0. Lymph nodes were the most common site of metastasis (38.5%) and 46.2% presented with ≥3 sites of disease. Clear cell pathology was reported in 96.2%.

**Discussion**

This retrospective study included group of patients with median age and sex distributions typically for RCC.

Inhibition of angiogenesis is a promising strategy for the treatment of clear-cell RCC [4, 21]. As clear-cell RCC overexpresses many cellular receptors related to angiogenesis, target agents such as sunitinib that affect
the activity of angiogenic growth factors show favourable results in the treatment of mRCC. Response rate of our study was 30.8%, comparable to that observed in other trials of sunitinib as first-line and second-line therapies [17, 18]. Many studies found that these rates are higher than that reported for chemotherapeutic agents or other cytokines [22-25].

Progressive disease was reported in 23%; this primary refractoriness may be explained by different pathogenesis including gene mutations with or without VHL (e.g. BAP1 and SETD2) [26-28].

PFS time in the range of 9.5–14.7 months has been observed in some trials [24, 29, 30], and in our study, it was 12 months.

In a phase II trial, there was no significant difference in safety between continuous or intermittent dosing of sunitinib [31].

Amongst non-haematological adverse events, fatigue was the most common one (50%) followed by diarrhoea (42.3%), then nausea and vomiting (38.4%) and hand-foot syndrome (27%) in our study. Adverse events of particular concern to patients were fatigue, gastrointestinal toxicity and hand-foot syndrome in other studies [17, 18, 32, 33]. However, in a study conducted by Motzer et al. [24], it was found that grade III or IV fatigue was significantly higher amongst patients received INF-α than those received sunitinib, but they reported higher haematologic adverse events in the sunitinib group; in this study, grade IV events were not observed.

**Table 2. Adverse events to sunitinib.**

| Adverse events | Grade | | | | | |
|---------------|-------|---|---|---|---|
|               | I  | II | III | I  | II | III |
| Neutropenia   | 5  | 3  | 2  | 19.2% | 11.5% | 7.8% |
| Anaemia       | 4  | 3  | 1  | 15.3% | 11.5% | 3.9% |
| Thrombocytopenia | 5  | 4  | 3  | 19.2% | 15.3% | 11.5% |
| Fatigue       | 5  | 6  | 2  | 19.2% | 23.1% | 7.8% |
| Diarrhoea     | 4  | 5  | 2  | 15.3% | 19.2% | 7.8% |
| Hand-foot syndrome | 3  | 3  | 1  | 11.5% | 11.5% | 3.9% |
| Rash          | 2  | 2  | 1  | 7.8%  | 7.8%  | 3.9% |
| Hypothyroidism| 1  | 1  | 0  | 3.9%  | 3.9%  | 0    |
| Mucositis     | 2  | 3  | 0  | 7.8%  | 11.5% | 0    |
| Pain in the limb | 2  | 0  | 0  | 7.8%  | 0     | 0    |
| Increased total bilirubin | 3  | 1  | 0  | 11.5% | 3.9%  | 0    |
| Nausea and vomiting | 4  | 5  | 1  | 15.3% | 19.2% | 3.9% |

**Table 3. Response rate.**

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response (PR)</td>
<td>8</td>
<td>30.8</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>12</td>
<td>46.2</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

![Figure 1. PFS amongst all studied cases.](image-url)
Conclusion

This study proved effectiveness and safety of sunitinib as first-line treatment for mRCC. However, this is a retrospective study and relatively small numbers of patients were included, so prospective studies with larger number of patients are needed for further evaluation.

Competing interests

The authors declare that they have no competing interests.

Informed consent: ‘Informed consent was obtained from all individual participants included in the study.’

Ethical approval: ‘All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.’

References


