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Original Research Paper

Oncology

COMPLETE REMISSION WITH TYROSINE KINASE INHIBITORS IN METASTATIC RENAL CELL CARCINOMA

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ABSTRACT We report a case of patient with disseminated metastatic clear-cell renal carcinoma (mCCR); who achieved radiological and metabolic complete response (CR) that lasted 3 years after starting Tyrosine Kinase Inhibitors therapy (TKI) with sunitinib then sorafenib . Durable clinical and pathological CRs are possible with targeted agents, even with disseminated metastases. Further researches are needed to define the optimal duration of systemic therapy in exceptional responders and identify the molecular determinants of response and resistance.

KEYWORDS : Metastatic renal cell carcinoma; TKI; Sunitinib; Sorafenib; Complete remission.

Introduction:

Targeted therapy including multi-tyrosine kinase inhibitors (TKIs) has upgraded the treatment of metastatic renal cell carcinoma (m RCC) (1). They significantly improved patient outcome in terms of progression-free survival and overall survival (1,2). Most patients achieve stable disease or partial response; the complete remission (CR) rate is much lower and has been reported to be about 3% with sunitinib in a phase III trial (1). CRs have primarily been described in case reports then in retrospectives series (3). The majority of patients received sunitinib, with or without surgical intervention (3). CR has been noted in many different metastatic sites, including lung, adrenal, hepatic, and pancreatic metastases (3). We report here a case of a patient who achieved a clinical and a radiologic CR after treatment with Sorafenib for disseminated RCC.

Case report:

A 65-year-old Moroccan woman with no personal medical historywas diagnosed with right RCC and underwent a right radical nephrectomy in 2012.Histological examination showed Clear-cell carcinoma of the kidney, grade 2 Fuhrman, p T2Nx and initially M0.Nine months later, she presented with dyspnea and chest pain. Computed tomography (CT) revealed spread pulmonary metastases (figure1).

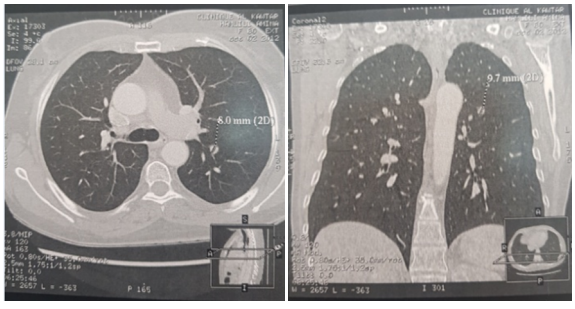

Figure 1: CT of the thorax: Pre-treatment scan shows a diffuse pulmonary metastases

She was therefore referred to our hospital for treatment. The disease was staged of good risk according to Hung classification. Sunitinib 50 mg daily 4 weeks on and 2 weeks off was started. A partial response then disease stability was objectived after 12 and 24 weeks of sunitinib respectively. Nevertheless, the patient experienced bad clinical and biological tolerance was noted: Grade 4 mycosis, peripheral edema and thrombocytopenia were noted. Given these adverse events, we discontinued Sunitinib and Sorafenib 400 mg twice daily was started.

The patient presented a complete radiological remission that was assessed in the positron emission-computed tomography (PET-CT) (figure 2).

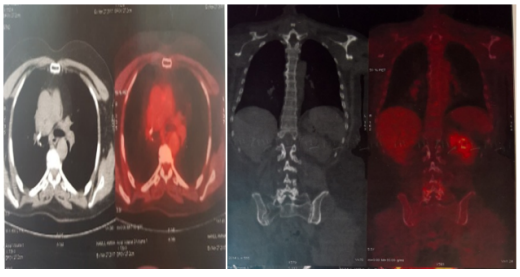

Figure 2: Whole body PET/CT show in the absence of uptake of the radiotracer fluorine-18 fluorodeoxy-glucose at the all volume explored

This remission lasted for 33 months. Then the patient experienced grade 3 asthenia, grade 2 diarrhea and grade 3 hand- foot syndrome. According to this issue and in consent with the patient, we interrupted the treatment. The patients' follow up showed no evidence of recurrence for 22 months.

Discussion:

Renal-cell carcinoma is the most common cancer of the kidney and accounts for 2-3% of all adult cancers worldwide (1). At diagnostic, up to 30% of patients presents with metastatic disease (1,2). The recurrences are developed in approximately 40% of patients treated for localized tumor (4). In Morocco, according to Rabat cancer registry, the incidence of kidney cancer from 2006 to 2008 was about 1% and 1.5% among females and males respectively (5).

Many molecular pathogenesis were identified in the last decade. The most important are Von Hippel LINDAU (VHL) gene mutation, deletion and alteration (2). Inactivation of VHL gene causes

persistent stimulation of the HIF-alpha that activates angiogenesis, tumor growth and metastases (4). Another pathway implicated in RCC is regulated by the mammalian target of rapamycin (mTOR).This pathway activates protein translation, angiogenesis and tumor cell proliferation (6). Understanding the molecular pathogenesis of RCC, allowed the development of many agents blocking the vascular endothelial growth factor (VEGF) pathway including tyrosine kinase inhibitors (eg, Cabozantinib, Pazopanib, Axitinib, Sunitinib, Sorafenib, Bevacizumab) (1,4,7–9) or the mTOR inhibitors (Temsirolimus, Everolimus) (6). This molecularly-targeted therapy improved patient outcome in terms of progression-free survival and overall survival in many phase III trials (3). In these studies patients achieved stable disease or partial response (3). The complete remission rate is much lower and has been reported to be about 3% with TKIs (1). It was achieved with both sunitinib and Sorafenib treatment (9,10).

In a retrospective study, including 64 patients treated with TKIs, a total of 36 patients experienced CR (3). After a median of follow-up of 13 months from CR, 53 patients had discontinued TKI therapy, whereas 11 patients continue to receive treatment with a TKI (3). A total of 29 patients (55%) who discontinued treatment remain without recurrence, with a median follow-up of 8.5 months (3). In our case after CR over than 14 months, we have decided to interrupt treatment.

In terms of the characteristics of patients achieving CR in several retrospective studies, the majority of patients were of favorable or intermediate risk (10–14). However, some patients with poor risk were also able to achieve CR (6). Our patient was with favorable risk, and remains free of disease during 22 months.

CR also seemed to be achieved regardless of the extent of the initial disease (15,16). It can be seen with patients with up to five metastatic sites (16). But no clinical or biologic parameters were identified to determine which patient is more likely to achieve CR in different studies because of their small samples (3,17,18). For the same reason, it was not possible to draw any conclusions about differences in relapse rates between patients who continued or stopped therapy (3,17,19). For our patient stopping treatment was supported by the long time of free disease survival and occurrence of severe side effects including fatigue gastro-intestinal and skin toxicities, whichwere affecting the patient's quality of life.

Conclusion:

TKIs are able to induce CRs; it was illustrated by several retrospectives analysis. We report here a case of a patient with metastases RCC who achieved a complete clinical and radiological response to Sorafenib. The patient continues to be disease-free close to 2 years after discontinuation of therapy. Our attitude was based on many series in the literatures,which showed that stopping treatment with a TKI after CR seen to be an acceptable optionespecially in patients with long-term stability, CR or severe toxicity, with a median time to progression of 10 months. Unfortunately no clinic-pathologic or biologic parameters were associated with achievement of CR in this retrospectives series. Furthermore in this same studies no factors to aid selection of patients who would be at less risk of recurrence after discontinuation of treatment. As such, further research is needed to identify those parameters.

Conflict of interest

There are no conflicts of interest.

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