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Assessment of Sunitinib Alternative Prescription Schedules in Metastatic Kidney Cancer: A Study of 10 Cases

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Abstract

Background: Managing metastatic Renal Cell Carcinoma (mRCC) has been revolutionized during the first decade of the 21st century due to the development of targeted therapies. The sunitinib is an oral multi–targeted receptor Tyrosine Kinase Inhibitor (TKI). It became the first targeted therapy as first–line treatment to improve the survival of patients with metastatic kidney cancer. This treatment consists in the oral intake of 50 mg of sunitinib per day in a 6 –week cycle including 4 weeks of treatment intake (the "on" week) followed by a 2–week break (the off week). The strong impact of the treatment dose reduction or discontinuation and the associated adverse effects encouraged the investigators to enquire about other sunitinib schedules: continuous regimen at 37.5 mg of sunitinib, 2 weeks out of 3 at the dose of 50 mg. The aim of this work is to assess the efficiency and the tolerance of the other prescription regimens of sunitinib

Methods: This is a transversal study conducted from March 2013 until November 2017 in the Oncology/ Hematology Center of the Med VI University Hospital Center in Marrakech. All patients under supervision and treatment for metastatic kidney cancer evaluated after 3, 6 and 9 months are part of our study. The parameters studies are epidemiological data, histological type, used protocols efficiency and tolerance.

Results: A total of 10 patients under supervision for metastatic kidney cancer were gathered in the Oncology/Hematology Center of the Med VI University Hospital Center in Marrakech. At the end of the 9–month evaluation period, 10 patients (40%) had radiological and clinical stability, 1 patient had complete lesion response, 3 patients had radiological progression and 1 case of death was recorded. As regards toxicity, all different regimen used during the study were well tolerated by the majority of the patients. The toxicities mostly encountered were asthenia, hand–foot skin reactions, mucositis and grade II diarrhea for 4 patients (40%) and 1 case of HTA. In only one case of temporary cessation vomiting and grade II diarrhea were noted.

Conclusion: The regimen 2/1 appears to be effective and demonstrates a better toxicity profile, treatment adherence, and dose intensity in relation to treatment, suggesting that the 2/1 regimen may become the future standard sunitinib treatment for patients with mRCC.

Keywords: Renal cell carcinoma, Sunitinib, regimen, Efficacy, Toxicity.

Introduction

Managing metastatic Renal Cell Carcinoma (mRCC) has been revolutionized during the first decade of the 21st century due to the development of targeted therapies. This type of tumor is marked by genetic damage in the von Hippel– Lindau (VHL) leading to the activation of numerous pro–angiogenic factors, such as the Vascular Endothelial Growth Factor (VEGF) and the Platelet Derived Growth Factor (PDGF) [1].

Sunitinib is an oral multi–targeted receptor Tyrosine Kinase Inhibitor (TKI) that inhibits VEGF receptors (VEGFR–1, VEGFR–2 and VEGFR–3). It became the first targeted therapy as first–line treatment to improve the survival of patients with metastatic kidney cancer [2–3]. Animal studies have shown that the drug total plasma concentration (sunitinib as well as its active metabolite) between 50 and 100 ng/ml was able to inhibit the PDGFR phosphorylation. This treatment consists in the oral intake of 50 mg of sunitinib per day in a 6 –week cycle including 4 weeks of treatment intake (the "on" week) followed by a 2–week break (the "off" week) according to

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a dosing regimen referred to as 4/6 [2–3]. The side effects included fatigue, hypertension and skin bullosa toxicity. On the biological side, hematologic disorders (anemia, leukopenia, thrombocytopenia, lymphopenia) were found in over 70% of the patients and hepatic cytolysis was detected for a least half of the patients [2–4]. During Phase III trials, these adverse effects were responsible for the reduction of the sunitinib dose for 32 to 52% of the patients, for a temporary treatment cessation for 38 to 49% of the patients and for a permanent discontinuation due to toxicity for 8–20% of the patients [2–4].

When significant and/or debilitating toxicity occurs despite the adapted supportive care provided, the primary strategy remains dose reduction [3]. However, keeping a maximum intensity dose seems to be linked to the improvement of overall survival, including time, disease progression and control rate.

The strong impact of the treatment dose reduction or discontinuation and the associated adverse effects encouraged the investigators to enquire about other sunitinib schedules: continuous regimen at 37.5 mg of sunitinib, 2 weeks out of 3 at the dose of 50 mg., etc.

The aim of this work is to assess the efficiency and the tolerance of the other prescription regimens of sunitinib

Patients and Methods

We conducted this study from March 2013 until November 2017 in the Oncology/Hematology Center of the Med VI University Hospital Center in Marrakech. All patients under supervision and treatment for metastatic kidney cancer evaluated after 3, 6 and 9 months are part of our study.

The administration regimen used was: 2 weeks on – 1 week off, continuous regimen of 37.5mg, 1week on– 1 week off. The study parameters were epidemiological data, histological type, used protocols efficiency and tolerance. Clinical evaluation was performed at three cycles. Tumor assessments, based on RECIST (version 1.1), were performed every 9 weeks. Adverse events were monitored regularly and were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

Statistical method

Descriptive data analysis was performed with the use of Excel 2010 software.

Results

A total of 10 patients under supervision for metastatic kidney cancer were gathered in the Oncology/Hematology Center of the Med VI University Hospital Center in Marrakech. The median age of our series is 53 years with extremes of age ranging from 20 to 80 years. We have not identified any significant difference between male and female with a male–to–female ratio of 1.

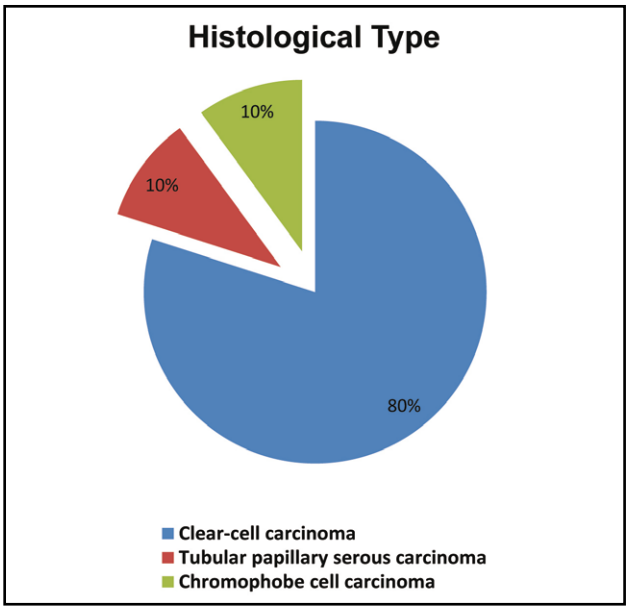

Figure 1. Patients distribution according to histological type

The clear–cell carcinoma was the predominant histological type in our study and was found in 8 patients (80%), followed by the tubular papillary serous carcinoma (1 patient) and the chromophobe cell carcinoma (1 patient). (Figure 1)

Protocols	Patients (Nos.)	Proportion (%)
Regimen 2/1	8	80
Continuous regimen of 37.5 mg	1	10
Regimen 1/1	1	10

Table 1: Patients distribution according to the different protocols

Evaluation after 9 months	Patients (Nos.)	Proportion %
Stable disease	4	40
Complete response	1	10
Radiological progression	4	40
Death	1	10

Table 2. Patients distribution according their evaluation after 9 months of supervision

Regimen	Toxicity
2 Weeks on/1 Week off	HTA, hypothyroidism, Asthenia grade 2
Continuous regimen **37.5 mg**	Asthenia grade3, Vomiting grade3, diarrhea grade 3
Regimen 1 Week /1 off	No toxicities

Table 3. Sides effects according to the regimens used

In our study, three regimens were used. The regimen 2 weeks on / 1 week off is the most used regimen (8 patients), followed by the continuous regimen of 37.5 mg and 1 week on / 1 week off. (Table 1)

At the end of the 9–month evaluation period, 10 patients (40%) had radiological and clinical stability, 1 patient had complete lesion response, 3 patients had radiological progression and 1 case of death was recorded. (Table 2)

As regards to toxicity, all different regimen used during the study were well tolerated by the majority of the patients. The toxicities mostly encountered were asthenia, hand–foot skin reactions, mucositis and grade II diarrhea for 4 patients (40%) and 1 case of HTA. In only one case of temporary cessation vomiting and grade II diarrhea were noted. (Table 3)

Discussion

Sunitinib has shown its efficiency on patients with mRCC and is currently the first–line standard in this localization [2]. This study was built in order to evaluate the efficiency and the tolerance of other sunitinib dosage and application modes. Nevertheless, how can we reach the best risk/benefits balance for each patient? Sunitinib alternative schedules may comprise a valid answer to this question. However, sunitinib dosage complexity is worth a careful assessment.

In our study, the median age was 53 years and clear cell carcinoma was the most frequent histology. These results are similar to those found by Bjanarsson et al and Motzer Rj et al [5,3].

Available data in the literature show that alterative sunitinib dosing regimens are feasible and allow to limit adverse effects along with preserving antitumor activity [5–8]. A sunitinib continuous dosing regimen with the reduced dose of 37.5 mg does not provide benefits in terms of toxicity and doses received. Moreover, the efficiency seems lower than the standard regimen [9–11].

In a retrospective study involving more than 600 patients with advanced solid tumors, gastrointestinal stromal tumors (GIST) or RCC treated with sunitinib, a direct collapse between the steady–state concentration of total active drug in plasma and TTP was found. Patients with mRCC with the greatest exposure to sunitinib demonstrated improved overall survival and better time to progression, greater likelihood of response and decreased tumor size, but also increased risk of adverse events [12]. In this meta–analysis of data from a Phase 2 study with sunitinib (4/2 protocol) on patients with mRCC, disease progression during treatment with sunitinib was also analyzed and showed that the concentration of cytokine and its active metabolite decreased to pre–dose levels during the 14–day resting period, suggesting a potential lack of drug exposure during which the tumor could progress. These data confirm a reversal of the desired pharmacodynamic effect during the 2 weeks in which the patients were off the drug and highlight the importance of starting sunitinib at the 50 mg dose and maintaining the dose intensity as high as possible while seeking an acceptable tolerance profile for the patient. But they do not address which dose / schedule achieves this goal more efficiently on patients with RCC.

In 2011, Riesenbeck et al proved that the development of hypothyroidism during sunitinib intake is an independent factor of PFS [13]. Thus in the same review Rini et al suggested that hypertension associated with sunitinib involves better clinical outcomes without increasing the adverse effects associated with hypertension [14]. Thus both hypothyroidism and hypertension have been suggested as clinical biomarkers of efficiency by supporting the design of the alternative treatment strategy based on escalating inter–patient doses, as far as tolerated until reaching one of these clinical efficiency markers.

Conclusion

Metastatic Renal Cell Carcinoma is a poor prognosis disease. Sunitinib is the standard of first line mRCC. The non–negligible side effects of sunitinib is responsible for the reduction of the dose. Choosing an ideal and individual regimen for each patient remains difficult due to the lack of biological knowledge that can facilitate the decision–making process. Despite the support of retrospective studies, regimen 2/1 appears to be effective and demonstrates a better toxicity profile, treatment adherence, and dose intensity in relation to treatment, suggesting that the 2/1 regimen may become the future standard sunitinib treatment for patients with mRCC.

Conflicts of interest

The authors do not declare any conflicts of interest

Contribution of authors

The authors participated in the management of the patients and the writing of the manuscript. The final version has been reviewed and approved by all authors.

References

1. Kaelin Jr WG. Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer .2002;2(9):673–82
2. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol .2009;27(22):3584–9.
3. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal–cell carcinoma.N Engl J Med. 2007;356(2):115–24.
4. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal–cell carcinoma. N Engl J Med 2013;369(8):722–31.
5. Bjarnason GA, Khalil B, Hudson JM, Williams R, Milot LM, Atri M,et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: correlation with dynamic microbubble ultrasound data and review of the literature. Urol Oncol 2014 May;32(4):480–7.
6. Neri B, Vannini A, Brugia M, Muto A, Rangan S, Rediti M, et al. Biweekly sunitinib regimen reduces toxicity and retains efficacy in metastatic renal cell carcinoma: a single–center experience with 31patients. Int J Urol 2013. May;20(5):478–83.
7. Atkinson BJ, Perpich J, Tannir NM, Jonasch E. Schedule modifications and treatment outcomes for sunitinib–related adverse events. JClin Oncol 2010; 28:e15115 (abstract).
8. Kletas V, Cheng W, Kollmannsberger CK, Law De Lemos M, Man S. A population–based analysis of overall survival associated with sunitinib given as intermittent, continuous, or nonconventional individualized dosing regimens for metastatic renal cell carcinoma. J Clin Oncol. 2013;31: e15541 (abstract).
9. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first–line therapy for advanced renal cell carcinoma. J Clin Oncol.2012;30(12):1371–7.
10. Escudier B, Roigas J, Gillessen S, Harmenberg U, Srinivas S, MulderSF, et al. Phase II study of sunitinib administered in a continuous once–daily dosing regimen in patients with cytokine–refractory metastaticrenal cell carcinoma. J Clin Oncol . 2009;27(25):4068–75.
11. Barrios CH, Hernandez–Barajas D, Brown MP, Lee SH, Fein L, LiuJH, et al. Phase II trial of continuous once–daily dosing of sunitinibas first–line treatment in patients with metastatic renal cell carcinoma. Cancer. 2012;118(5):1252–9.
12. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta–analysis. Cancer Chemotherapy Pharmacol. 2010 ;66(2):357–71.
13. Riesenbeck LM, Bierer S, Hoffmeister I, Köpke T, Papavassilis P, HertleL, et al. Hypothyroidism correlates with a better prognosis in metastaticrenal cancer patients treated with sorafenib or sunitinib. World J Urol .2011;29(6):807–13.
14. Rini BI, Melichar B, Ueda T, Grünwald V, Fishman MN, Arranz JA,et al. Axitinib with or without dose titration for first–line metastaticrenal–cell carcinoma: a randomised double–blind phase 2 trial. LancetOncol 2013; 14(12):1233–1242.