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Safety and Efficacy of Sunitinib for Metastatic Renal Cell Carcinoma in Indian Population: A Tertiary Care Center Experience

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Abstract

Purpose: Our study aims to evaluate the efficacy & safety of targeted therapy (Sunitinib) for metastatic renal cell carcinoma (mRCC) in Indian population. *Methods:* The hospital records of total ninety four patients were reviewed retrospectively in this study who were offered sunitinib for mRCC between 2008 to 2015. Out of ninety four patients 16 pateints (neo-adjuvant cases) were excluded and 78 were included in this study. All patients received Tyrosine kinase inhibitor, sunitinib therapy (50 mg OD, 4/2 scheme). All 39 patients underwent radical nephrectomy prior to initiation of sunitinib therapy. Patients were followed up every cycle for their clinical symptoms following sunitinib therapy and at every 3 month with chest Xray, ultra-sonography and bone scan, CT scan (if required). The RECIST criterion was used to evaluate the overall tumor response. *Results:* The median survival was 28.5 months (range 9.253-47.7) and progression free survival (PFS) was 9.16 months (range 6.08-12.23). Clear cell histology was found in 60 (76.9%) patients, papillary variety in 12 (15.39%) patients, chromophobe type was seen in 2 patients and rest had mixed sarcamatoid papillary and rhabdoid clear cell variety. Forty eight patients (61.5%) had multiple metastases. Most frequent metastasis was seen in lungs in 28 patients (36%) and bone in 24 patients (31%). Metastasis was also seen in draining lymph nodes, adrenal, omentum, skin, liver, brain. *Conclusion:* In our study, use of sunitinib showed similar outcome to previously published articles. Our study supports the use of sunitinib in metastatic renal cell carcinoma.

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Introduction

Renal cell carcinoma (RCC) accounts 90-95% of all renal neoplasm and 3% of adult malignancy [1,2]. Every year 100,000 patients die of RCC worldwide and the incidence is increasing by 2-3% per decade [1,3]. Prognosis of metastatic RCC is grim [4].This poor prognosis of mRCC is mainly due to multiple metastasis at presentation in about 95% pateints & resistant to treatment [10]. It is estimated that only 23% of the patients with mRCC will live for 5 years [5,6].

For Metastatic RCC traditional therapy include surgery of the primary and concomitant metastases when possible and immunotherapy and/or targeted therapy in patients with good performance status [6]. RCC is a difficult disease to treat when it presents with advanced features and for this reason correct staging is crucial for effective treatment. Advanced RCC has been treated historically with different cytokines & immunotherapy like interleukin- 2. Interferon alfa was also used but many patients could not tolerate the serious toxicities and only a smaller percentage of patients achieved complete response which was not durable [6].

The introduction of molecular targeted therapy like vascular endothelial growth factor (VEGF) neutralizing antibody (bevacizumab) and the VEGF receptor and platelet derived growth factor (PDGF) receptor targeted tyrosine kinase inhibitors (TKIs) (sorafenib, Sunitinib, pazopanib) has revolutionized the treatment of this disease. TKIs are known to have effects on tumor vascularity, angiogenesis processes and have direct effects on the tumor cells leading to significant reduction in tumor size in many cases. Sunitinib has been found

to have as high as 30% partial response rate using RECIST criteria for tumor measurement [7].

Methods

Hospital records were reviewed of all the patients who have been offered sunitinib for mRCC from 2008 - 2015. Out of the total ninety four patients, 16 were excluded and 78 were included in this study. All patients in this study received TKI's, sunitinib as the first-line treatment (50 mg once daily with a 4/2 scheme). All patients underwent Radical Nephrectomy prior to sunitinib except for 16 patients who had sunitinib as neoadjuvant prior to Nephrectomy and hence were excluded from the study.

In this study sunitinib was started after 2 weeks of surgery after removal of sutures and healing of wound. Patients were followed every month and relevant investigations were performed before starting each cycle. Complete blood count, liver, renal & thyroid functions tests were performed and sunitinib related complications were noted. Relevant treatment was instituted for complications and dose adjustment was made as required. Chest Xray and Ultrasound (USG) of abdomen was performed every three months and CT scan of abdomen and chest as required after evaluating chest xray and USG.

RECIST criteria version 1.1 was used to evaluate the overall tumor response.

Table 1 describes the patient's demographics and characteristics of the disease. Complications related to sunitinib were recorded and the regimen was either changed/discontinued or the dose was reduced. Table 2 shows the regimen-related complications.

Primary tumor of the kidney was described when found at the anatomical site without previous resection and when the tumor appeared at the previously

Table 1: Patient's demographics and characteristics of the disease

Characteristics		Number of patients (n)	Percentage (%)
Total Patients		78	
Range		31-80 yrs	
Sex	Male	60	76.9%
	Female	18	23.1%
Presentation	Primary tumor symptoms	Pain /heaviness/mass Hypochondrium	
	Metastatic tumor Symptoms	Back /bony pain, loss of weight, apetite, cough, paraperesis	
	Site	Right kidney(50)	64.1%
Metastatic Sites	Lung	28(36%)	
	Bone	24(31%)	
	Lymphadenopathy	10	
	Omentum	4	
	Adrenal	6	
	Liver	2	
	Skin	2	
	Brain	2	
	Thrombus	RV 4, IVC 6, lt atrium	
Sites(Metastases)	> 1	48(61.5%)	
	1	30	
Histology	Clear cell	60(76.9%)	
	Papillary	12(15.39%)	
	Chromophobe	2	
	Sarcomatoid	With papillary 4,clear cell 2, rhabdoid with clear cell 2	

Table 2: Complications of the Regimen

Complication	Number of Patient (n)	Percentage (%)
Genaralized weakness	38	51.28%
Hyponatremia	12	17.94%
Hand to mouth syndrome	28	35.89%
Cytopenia	32	41.02%
Neutropenia	16	20.5%
Thrmbocytopenia	10	12%
Anaemia	4	5%
Hypothyroidism	16	25.64%
Hypertension	4 severe	5.1%
Skin Lesions	20	25.64%
Diarrhoea	6	7.6%

resected tumor bed. Recurrence and metastasis was defined as tumor away from tumor bed during the course of the treatment.

Statistical Analysis

SPSS, Inc., Chicago IL (statistical package for the social sciences software ver.12) was used for the statistical analysis. PFS (progression free survival), Crude OS (overall survival), CSM (cause-specific mortality), LC (local control) were evaluated.

Results

Ninety four patients with mRCC were treated with Sunitinib. Sixteen patients had received sunitinib as neo-adjuvant therapy and were excluded from the study. Seventy eight patients received 50mg sunitinib once daily on 4 weeks on and 2 weeks off scheme. The age of the patients ranged from 31-80 years and there were 60 male (76.9%) and 18 female (23.1%) patients. One to twenty seven cycles of sunitinib were prescribed for a median of 4 cycles and mean of 5.2 cycles. Majority of the cases presented with primary tumor symptoms like pain/heaviness and mass at hypochondriac and some patients had meatstatic tumor symptoms like back/bony pain, loss of weight and appetite, cough and two patients presented with paraperesis. Right renal involvement (n-50, 64.1%) was commoner.

The median survival was 28.5 months (range 9.253 - 47.7) and progression free survival (PFS) was 9.16 months (range 6.08-12.23). According to the RECIST criteria, stable disease was found in 12 patients till date and complete response was document in 4 patients. Clear cell histology was found in 60 (76.9%) patients, papillary variety in 12 (15.39%) patients, chromophobe type was seen in 2 patients and rest had mixed sarcamatoid papillary and rhabdoid clear cell variety. Fourty eight patients (61.5%) had multiple metastasis. Most frequent metastasis was seen in lungs in 28 patients (36%) and bone in 24 patients (31%). Metastasis were also seen in the draining lymph nodes, adrenal, omentum, skin, liver, brain.

Table 3: TKI (Sunitinib) Therapy

27 cycles (2 patients)	Stable (complete remission)
25 cycles (2 patients)	Stable (complete remission)
19 cycles (2 patients)	Stable
15 cycles (2 patients)	Stable
11 cycles (2 patients)	Stable
8 cycles (2 pateints)	stable
6 cycles (14 patients)	Progression of disease
5 cycles(6 patients)	Progression of disease
4 cycles (20 patients)	Progression of disease
3 cycles (16 pateints)	Progression of disease
2 cycles (22 patients)	Progression of disease
1 cycle (4 patients)	Progression of disease

Total 94 patients, Excluded (neoadjuvant) 16 patients, Grand total on adjuvant sunitinib (78 patients)

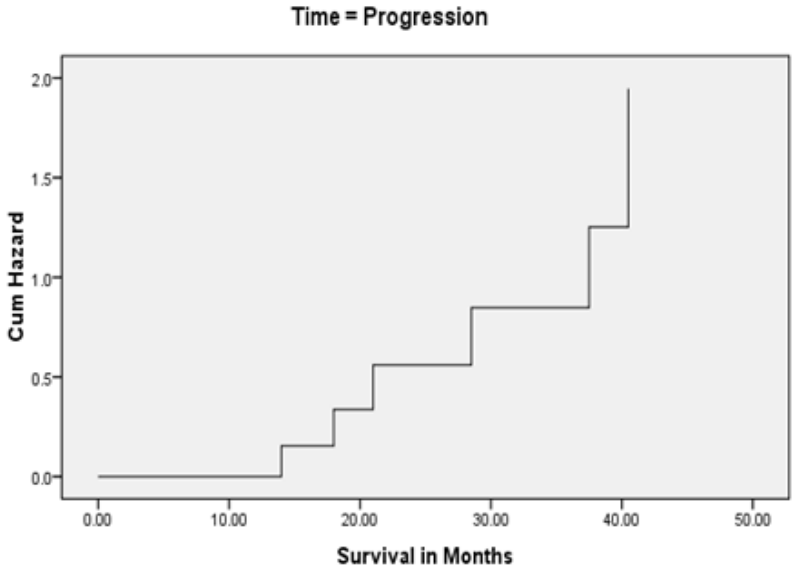

Fig. 1: Hazard Function

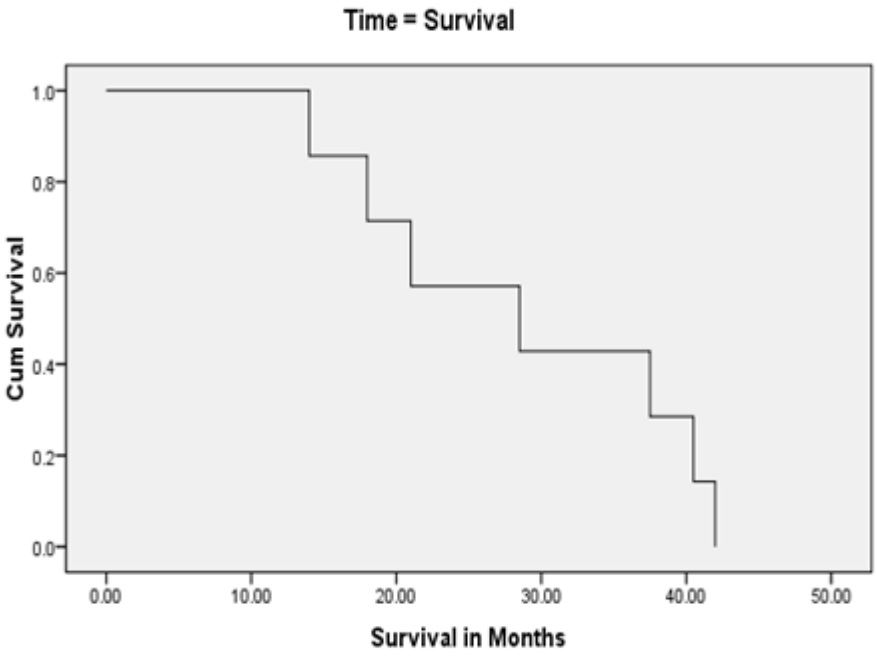

Fig. 2: Survival Function

Discussion

Renal cell carcinoma is a chemo-resistant tumor and is one the most lethal of all the common urologic tumors. Approximately 40% of the patients die of this disease [8,9]. Curative and /or curative intent surgical management is the choice for localized disease but about 25% will present with locally advanced and 20% to 30% will have systemic recurrence after treatment for localized disease [10]. In the past few years, there has been a shift in the management of RCC with the introduction of TKIs, VEGF antibodies and mTORS. A combination of surgery and targeted therapy is now being practiced increasing for locally advanced and mRCC and more recently these agents are used in a neoadjuvant settings [11]. Of the several anti-VEGFs some are sorafenib, sunitinib and pazopanib. In addition, bevacizumab, an anti VEGF antibody, also was approved in combination with IFN. mTOR inhibitors, temsirolimus was approved in patients with mRCC who presented with three out of six poor prognostic risk factors and everolimus for patients who failed first line drug like an anti VEGF therapy [12].

The tumor cells may secrete pro-angiogenic growth factors, like VEGF, PDGF, fibroblast growth factor and removing the primary tumor may remove the source of these factors and limit future metastasis. The use of TKIs inhibit some of the effects of these factors and decrease angiogenesis within metastasis when used as a neoadjuvant or adjuvant therapy [11,13]. Among TKIs sunitinib is widely used for the treatment of mRCC. Patients on sunitinib were reported to have objective tumor response of 39% and 6 % for the IFN. Grade 3-4 toxicities observed were acceptable with neutropenia (12 %), thrombocytopenia (8%), hypertension (8%), diarrhea (5%), hand to foot syndrome (5%) in the sunitinib arm [14].

The sunitinib expanded access programme included 490 patients which were given sunitinib as the first line systemic therapy. This study demonstrated a PFS of 12 months and 6.5 months in prior nephrectomy and without prior nephrectomy group respectively [15].

Jonasch et al. demonstrated a median PFS of 11.0 months and median OS of 25.4 months in patients treated with bevacizumab for mRCC [16]. In another study conducted by C. Seidel et al. showed median PFS of 8.7 months for patients with mRCC treated with TKI, sunitinib [17].

In Phase 2 trial by Motzer et al, sunitinib was given as 50 mg/ day for 4 weeks on & 2 weeks off for 6 weeks cycles to patients with cytokine refractory mRCC. Objective response of 40% with partial response in 25 out 63 patients was demonstrated and reduction in tumor size was noted in more than 70% of the patients.

The grade 3 toxicities in the above trials were fatigue (8-11%), nausea or diarrhea (3% to 6%), dermatitis such as hand /foot syndrome (3 to 7%), stomatitis (2 to 5%), hypertension (21 to 6%), lymphopenia (32%), neutopenia (13%), anemia (60 to 18%), thrombocytopenia (0 to 6%) [18].

In our cohort of patients 50 mg/day sunitinib (4/2week scheme) was prescribed. The most common side effect encountered was fatigue (51.28%) followed by hand to mouth syndrome (35.9%), hypothyroidism (25.64%), hyponatraemia (17.94%) were also observed in patients (Table 2). In our analysis, patients with

mRCC responded to sunitinib with favorable median PFS and OS as compared to noted studies. With a median PFS of 9.16 months (CI 6.08-12.23) (range2.5-35.5), our patient cohort had reasonable median OS of 28.5 months (CI 9.253-47.7). Twelve of the total patients are still on sunitinib with stable disease and out of which four patients are having complete response. PFS and median OS are expected to increase in our study. The safety and efficacy of suinitinib in Indian population is acceptable and comparable with existing western world literature.

Conclusion

Suinitinib is safe and effective in Indian population when used as first line TKI for mRCC.

References

1. Gupta k, Miller JD, Liz 2, Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (m RCC) a literature review. Cancer Treat rev. 2008;34:193-205.
2. Jemal A, Siegal R, Ward E, Haoy. Cancer Statistics. Cancer J Clin 2009;59:225-49.
3. Basso M, Cassano A, Barone. A survey of therapy of advanced renal cell Carcinoma. Urol Oncol. 2009;28: 121-33.
4. NCCN clinical practice guide line in oncology. Kidney cancer V. 2, 2010, National comprehensive cancer network website. http //www.nccn.org/professionals/ physicians/pdfkidneypdf.accessed feb 2010.
5. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factor for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454–63.
6. Ather MH, Masood et at. Current management of advanced and metastatic renal cell carcinoma. Urol J 2010;7:1-9.
7. C Motzer RJ et al. Sunitinib verses interferon in metastatic renal cell carcinoma. N Eng J Med 2007;356:115-24.
8. Janzen NK et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol clin North Am. 2003;30:843-52.
9. Brian R et al. Targeted Molecular therapy for renal cell carcinoma. Urology. 2007;69:3-10.
10. Janzen NK et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol clin North Am. 2003;30:843-852.
11. Alex Bex, Eric Jones et al. Integrating surgery with Targeted therapy for renal cell carcinoma. Current evidence and ongoing trials. European Urology 2010; 58:819-28.
12. Mozter RJ Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma. A double blind randomized placebo controlled phase III trials. Lancet 2008;372:449-56.
13. Slaton JW, Perrotte et al. Expression levels of genes that regulate metastasis and angiogenesis correlate with advanced pathologic state of renal cell carcinoma Am j pathol 2001;158:735-43.
14. Motzer RJ, Tomczak P et al. Sunitinib vs interferon alfa metastatic renal cell carcinoma. N Eng J Med 2007;356: 115-124.
15. Szczlik C et al. Sunitinib in patients with or without prior nephrectomy in an expanded access trial of metastatic renal cell carcinoma (mRCC). J Clin Onc 2008;26(may 20 suppl):124.
16. Jonasch et al. Phase II presurgicl feasibility study of bevacizumab in untreated patients with metastaic renal cell carcinoma. J Clin Onc 2009;27(25):4076-4081.
17. C. Seidel et al. Response of renal lesions during systemic treatment with sunitinib in patients with metastatic renal cell carcinoma.a single centre experience in 14 patients. World J rol (2011)29:355-360.
18. Motzer RJ, Michaelson MD, et al. Phase 2 trials of SU11248 show anti tumor activity in second line therapy for patients with metastatic renal cell carcinoma (RCC). Proc AM Soc Clin Oncol 2005;23:4508.