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Treatment outcomes of metastatic nonclear cell renal cell carcinoma: A single institution retrospective analysis

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Abstract

Introduction: Nonclear cell (NCC) metastatic renal cell carcinoma (mRCC) is a biologically heterogeneous entity. We report the outcomes of NCC mRCC treated with first-line vascular endothelial growth factor (VEGF) inhibitors or mammalian target of rapamycin (mTOR) inhibitors at our institute. This is first such report from India. **Methods:** This is a retrospective analysis of the 40 consecutive patients of NCC mRCC treated between January 2013 and June 2015 in routine clinical practice at our institute. The primary endpoint analyzed was overall survival (OS) with respect to the type of first-line treatment and tumor histology. **Results:** The most common histological subtype was papillary in 25 patients (62.5%) followed by sarcomatoid in six (15%), chromophobe in 5 (12.5%), translocation-associated in one patient, and other nonspecified in three patients. First-line treatment was sorafenib in 14 (35%), sunitinib in 9 (22.5%), pazopanib in 8 (20%), everolimus in seven (17.5%), and best-supportive care (BSC) in two (5%) patients. Partial response, stable disease, and progression was observed in six (15%), 13 (32.5%), and nine (22.5%) cases, respectively, as the best response to first-line treatment. The median OS was 11.7 months and median event-free survival was 6.1 months in the whole cohort. The median OS in months for different first-line treatments were as follows: sorafenib (16.2), sunitinib (11.7), pazopanib (not reached, mean-23.9 ± 6.0), everolimus (4.1) and BSC (0.6) and for different histological subtypes were as follows: papillary (9.8), chromophobe (not reached, mean-30.3 ± 8.4), sarcomatoid (4.1), and others (7.9). **Conclusions:** Chromophobe histology has a better outcome compared to other histological subtypes, and anti-VEGF tyrosine kinase inhibitors are preferable first-line agents compared to mTOR inhibitors.

Key words: Chromophobe, metastatic, nonclear cell, papillary, renal cell carcinoma, sarcomatoid

Introduction

Nonclear cell (NCC) renal cell carcinoma (RCC) comprises about 25% of all renal cancers.[1] These renal cancers are known by their morphology, growth pattern, a cell of origin as well as the histochemical and biologic basis that characterize them. The main subtypes of NCC RCC include: papillary (10%–15%), chromophobe (5%), collecting duct (1%–2%), and unclassified (5%). Other rare subtypes are translocation-associated (<1%) and medullary carcinomas (<1%). Sarcomatoid variant is also often included in NCC RCC; although, it is not a distinct subtype and can be seen in any histologic type.[2,3]

Advances in the treatment of metastatic RCC (mRCC) is largely limited to clear-cell histology as the majority of studies until date have excluded patients of NCC types.[4] There is no universally accepted treatment strategy for NCC mRCC due to the paucity of published quality research vis-à-vis clear cell type. Excluding collecting duct and medullary carcinomas, where chemotherapy on the lines of urinary bladder cancer have shown considerable responses,[5] treatment strategy of NCC mRCC mirrors that of clear cell RCC utilizing angiogenesis inhibitors and molecular targeted agents.

The largest retrospective data come from a systematic review and meta-analysis of 20 studies that included 1244 patients of NCC mRCC on targeted therapy showing lower objective response rate (ORR) (9.2% vs. 14.8%), progression-free survival (PFS) (7.5 m vs. 10.5 m) and overall survival (OS) (13.2 m vs. 15.7 m) compared to 6300 patients of clear cell type.[6] Data from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) also showed that NCC mRCC patients had a significantly worse OS than their clear cell counterparts (12.8 m vs. 22.3 m).[7] The largest prospective data are from the ASPEN trial, a Phase-II comparative study which included 108 patients of NCC mRCC. Results showed a longer median PFS with first-line sunitinib versus everolimus (8.3 m vs. 5.6 m, $P = 0.16$, heart rate1.41). In good and intermediate-risk patients in the study, sunitinib was found to be better while in poor risk subset everolimus had a longer PFS (6.1 m vs. 4 m).[8] The RECORD-3 study also showed a trend toward longer PFS with initial sunitinib compared with everolimus (7.2 m vs. 5.1 m) in the 66 patients who belonged to the subset of NCC mRCC.[9] The ESPN crossover study, however, showed no difference in OS between initial sunitinib and everolimus (16.2 m vs. 14.9 m).[10]

In this study, we report here the outcomes of NCC mRCC treated with vascular endothelial growth factor (VEGF) inhibitors or mammalian target of rapamycin (mTOR) inhibitors at our institute, a tertiary care referral cancer center in India. To the best of our knowledge, this is first such report from India.

Methods

This is a retrospective analysis of a prospectively maintained database of 40 consecutive patients of NCC mRCC who were treated with first-line VEGF/mTOR inhibitors in the Department of Medical Oncology at our institute. We included patients who started treatment from January 2013 to June 2015. Patients who had received any prior therapy, including chemotherapy, targeted therapy, or cytokine therapy were excluded from the study. We also excluded patients of collecting duct carcinoma and renal medullary cancers as they were treated with gemcitabine and platinum-based chemotherapy upfront. Data were obtained from the hospital electronic medical records and case files. Written informed consent was obtained from

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each patient before starting treatment. Patients were treated with either a tyrosine kinase inhibitor (TKI) (sunitinib, sorafenib, and pazopanib) or mTOR inhibitor (everolimus) as per clinician and patient preference. Treatment was started at standard doses as per guidelines and continued until disease progression or unacceptable toxicity as per clinician's judgment. Supportive care included monthly zoledronic acid for bone metastasis and palliative radiotherapy if required. They were followed-up in the outpatient department as per routine clinical practice. Response evaluation was done every 2–3 months with scan or as and when required as per clinician's discretion. Response to treatment was based on clinical assessment and radiology as per RECIST 1.1 criteria.

Ethics committee approval was not required as it was a retrospective audit. The analysis was performed in August 2016. The primary endpoint analyzed was OS with respect to the type of first-line treatment and tumor histology. Secondary endpoints were best ORR and event-free survival (EFS). EFS was calculated as the time between the start of therapy and the date of progression, change of treatment due to any reason, or death from any cause. EFS and OS were calculated using Kaplan–Meier method. Statistical measures were calculated using software IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Results

The median age of the 40 patients was 50.5 years. The baseline demographic and clinical characteristics, tumor features including histology, metastasis number and location, and the risk group stratification as per the Heng's and Motzer's model, of the study population are listed in Table 1. Papillary carcinoma (62.5%) was the most common NCC mRCC encountered followed by sarcomatoid variant (15%) and chromophobe histology (12.5%). There were three cases which could not be classified into any histological subtype of renal cancer as the diagnosis was by cytology. The most common site of metastasis was lung (62.5%), followed by bone (40%), liver (22.5%), and brain (7.5%) with 40% having more than one metastatic site.

The primary and secondary outcome analysis as per the first-line treatment and histology is documented in Tables 2 and 3, respectively. The mean duration of follow-up was 11.8 months. The median EFS of the whole cohort was 6.1 months, and median OS was 11.7 months. The overall clinical benefit rate (partial response [PR] + stable disease [SD]) of TKI was 68% among all evaluable patients for response assessment (17 out of 25). Response evaluation every 2–3 months was not available for 12 patients (30%), for whom the best objective response could not be evaluated. At the time of analysis, 26 out of 40 patients were dead and 10 were alive (6 on primary therapy with TKI and 4 on best supportive care postprogression), and four patients were lost to follow-up. At the time of analysis, there were a total of 30 patients who ultimately had disease progression, among whom only four were surviving compared to six patients who did not have disease progression on first-line TKI, all of whom were alive. Only 10 patients received 2nd line treatment (6 received another TKI, and 4 received everolimus), and subgroup analysis showed improved median OS with 2nd line treatment compared to those who did not get any treatment postprogression (Not reached vs. 8.6 months).

Table 1: Baseline patient characteristics

Baseline characteristics	Numbe of patients (n=40; 100%)
Age (years)	
<65	34 (85)
≥65	6 (15)
Sex	
Male	31 (77.5)
Female	9 (22.5)
Comorbidities	17 (42.5)
Hypertension	11 (27.5)
Diabetes	3 (7.5)
Viral hepatitis	2 (5)
History of smoking	
Yes	6 (15)
No	34 (85)
Previous nephrectomy	
Yes	17 (42.5)
No	23 (57.5)
Median hemoglobin (g %)	12 (7-15)
Histology	
Papillary	25 (62.5)
Chromophobe	5 (12.5)
Sarcomatoid	6 (15)
Translocation associated	1 (2.5)
Others	3 (7.5)
ECOG performance	
0	4 (10)
1	23 (57.5)
2	9 (22.5)
3	3 (7.5)
4	1 (2.5)
Number of metastatic sites	
1	24 (60)
≥2	16 (40)
Site of metastasis	
Lung	25 (62.5)
Bone	16 (40)
Liver	9 (22.5)
Brain	3 (7.5)
Heng's risk group	
Low	8 (20)
Intermediate	18 (45)
High	12 (30)
Not known	2 (5)
Motzer's risk group	
Low	9 (22.5)
Intermediate	14 (35)
High	13 (32.5)
Not known	4 (10)

ECOG: Eastern Cooperative Oncology Group

Figures 1 and 2 show the Kaplan–Meier graph for OS as per the first-line treatment and histology, respectively. However, the differences in outcome did not reach statistical significance.

In a subset analysis, the initial response to therapy and low-risk disease by both Heng's and Motzer's model had better OS while initial progression on therapy and high-risk disease worsened OS. However, the results were not statistically significant. Median OS corresponded to Heng's risk stratification model– low risk– 27.1 months, intermediate risk– 10 months and high risk– 7.7 months [Figure 3].

Table 2: Primary and secondary outcome results as per first-line treatment

End points	Sorafenib (*n*=14; 35%)	Sunitinib (*n*=9; 22.5%)	Pazopanib (*n*=8; 20%)	Everolimus (*n*=7; 17.5%)	Best supportive care (*n*=2; 5%)	Overall (*n*=40; 100%)
Best objective response						
CR	0	0	0	0	-	0
PR	1 (7)	1 (11)	4 (50)	0	-	6 (15)
SD	5 (37.5)	5 (55.6)	1 (12.5)	2 (28.5)	-	13 (32.5)
PD	4 (28.6)	2 (22)	2 (25)	1 (14)	-	9 (22.5)
Not known	4 (28.6)	1 (11)	1 (12.5)	4 (57)	2 (100)	12 (30)
Median EFS (Months)	7.7	9.6	8.6	3.4	0.7	6.1
Median OS (months)	16.2	11.7	NR	4.1	0.7	11.7

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, EFS: Event-free survival, OS: Overall survival

Table 3: Primary and secondary outcome results as per histology

End points	Papillary (*n*=25; 62.5%)	Chromophobe (*n*=5; 12.5%)	Sarcomatoid (*n*=6; 15%)	Translocation associated (*n*=1; 2.5%)	Others (*n*=3; 7.5%)
Best objective response					
CR	0	0	0	0	0
PR	4 (16)	0	1 (16.7)	0	1 (33)
SD	10 (40)	3 (60)	0	0	0
PD	5 (20)	1 (20)	1 (16.7)	1 (100)	1 (33)
Not known	6 (24)	1 (20)	4 (66.7)	0	1 (33)
Median EFS (months)	8.6	13.1	3.6	7.8	3.1
Median OS (months)	9.8	NR	4.17	21.4	7.9

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, EFS: Event-free survival, OS: Overall survival

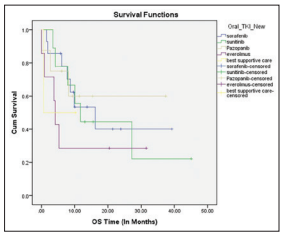

Figure 1: Kaplan–Meier graph showing median overall survival of nonclear cell metastatic renal cell carcinoma patients stratified as per different first-line treatments

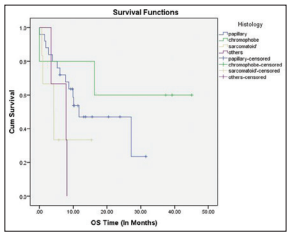

Figure 2: Kaplan–Meier graph showing median overall survival of nonclear cell metastatic renal cell carcinoma patients stratified as per different histologies

The subset of papillary mRCC was also analyzed separately as per different first-line treatments. Sunitinib had the longest EFS of 10 months [Figure 4].

Discussion

NCC mRCC is a rare and heterogeneous entity with diverse prognoses and responses to treatment. Most of the landmark trials that led to the approval of targeted agents in advanced RCC excluded patients with NCC RCC except the Global RCC trial with temsirolimus versus interferon versus the combination where 20% of patients had NCC histologies.[11] High-quality evidence from phase-III randomized studies to guide management decisions for patients with NCC mRCC is lacking. Available data on the use of targeted therapy in NCC mRCC are based on retrospective cohorts,[7] a few single-arm[12-15] as well as comparative[8,10] phase-II studies and expanded access programs.[16,17] Only a few small retrospective studies have been published describing the outcomes of NCC mRCC after treatment with sunitinib, sorafenib, and pazopanib.[18-20]

The histological subtype distribution in the study as well as the median OS/EFS matches well with the described literature reflecting minimum selection bias in the study.[6,7] Among different histological subtypes after nephrectomy for localized disease, papillary cell subtype portends a favorable prognosis compared with clear-cell RCC, while metastatic papillary RCC has poorer survival.[21] Two distinct classes of papillary RCC exist, based on separate morphologic and molecular features defined by alterations in the *c-Met* oncogene (type 1) or the fumarate hydratase gene (type 2).[22,23] These two classes have different outcomes with type 2 papillary mRCC being the most aggressive.[24] We did not stratify patients of papillary mRCC in our study according to these two histologic subtypes as in most other studies. Hence, the results described in the literature have been inconsistent. In the SUPAP study, in type 1 papillary mRCC, 2/15 (13%) patients had a PR, 10 had SD while in type 2, 5/45 (11%) patients had a PR, 25 had an SD.[25] The median PFS was 6.6 months in type 1, and 5.5 months in type 2. The median OS was 17.8 and 12.4 months, respectively, in type 1 and type 2. In another study, a retrospective multi-institutional one, two (4.8%, both on sunitinib) of 41 papillary mRCC patients achieved a response. PFS for the whole cohort was 7.6 months. Sunitinib-treated patients had a PFS of 11.9 months compared with 5.1 months for sorafenib-treated patients ($P < 0.001$).[19] The European (EU) ARCCS trial, an open-label, noncomparative phase-III study that included 118 patients with metastatic papillary RCC on sorafenib, of whom 104 were evaluable for response, the disease control rate was 66.4%, and the median PFS was 5.8 months.[26] In this study, among the 25 patients of papillary mRCC, 19 were evaluable for response. Partial response was achieved in four patients while 10 had SD as the best response, with an overall clinical benefit of 73%. Sunitinib had the longest median EFS of 10 months followed by 7.7 months with sorafenib [Figure 4].

For chromophobe histology, both VEGF TKIs and mTOR inhibitors appear to have some activity. In one study that included 12 patients with chromophobe RCC, three (25%) patients achieved a response (two patients treated with sorafenib and one

treated with sunitinib), and median PFS was 10.6 months.[19] In the ASPEN study, the median PFS in the chromophobe subset was 5.5 months in sunitinib arm while 11.4 months in everolimus arm.[8] In the ESPN study, patients with chromophobe RCC achieved a longer median OS (31.6 months in the sunitinib arm and 25.1 months in the everolimus arm).[10] In our study, among the four evaluable patients of chromophobe mRCC patients for best response, three patients had stable disease. Median EFS was 13.1 months; median OS was not reached and mean OS was 30.3 ± 8.4 months.

Sarcomatoid variant of mRCC is universally associated with a poor prognosis, with a median OS of 2–9 months.[27,28] In the IMDC, a total of 230 patients were identified with sarcomatoid features. Approximately 93% of patients received VEGF-directed therapy in the first-line setting, and the overall response rate was 21%. The median PFS and OS were 4.5 and 10.4 months, respectively. In our study, patients with sarcomatoid mRCC had poor outcome with a median EFS of 3.6 months and median OS of 4.2 months.

Comparing different treatment arms in our study– the PR rate was 19% (6 out of 31 patients with PR) with TKI compared to none with everolimus. The seven patients who were on first-line everolimus fared poorly with a median EFS of 3.7 months and median OS of 4.1 months, although all patients belonged to high-risk category. The superiority of TKI over everolimus in our study results goes in tandem with the ASPEN and RECORD-3 data,[7,8] although the median EFS in our cohort was much lower. This can be due to poor tolerance and dose-intensity of everolimus in Indian patients. Among TKI, there were four out of eight patients (50%) who achieved PR with pazopanib while one patient had stable disease. Patients on pazopanib had median EFS of 8.6 months while median OS was not reached (mean OS 23.9 ± 6 months). The results with pazopanib are comparable to the recent retrospective study published by *Matrana et al.,* where nine patients of NCC mRCC on the first-line pazopanib were analyzed.[20] In their cohort, 33% had PR, median PFS was 8.1 months, and median OS was 31 months. Sunitinib had the longest median EFS of 9.6 months in our study, but shortest median OS of 11.7 months. However, none of the patients on first-line sunitinib received second-line treatment. Further prospective trials should evaluate if pazopanib is superior to sunitinib in NCC mRCC.

Subgroup analysis showed that patients having an initial response to TKI and those who received second-line therapy had better OS compared to those with initial progression and those who did not receive second-line therapy. Furthermore when median OS of the whole cohort was stratified according to risk stratification as per both Heng's and Motzer's model, there was separation of the curve between the three risk-groups as shown in Figure 3, showing the validity of these models in NCC mRCC. In a retrospective study by Kroeger *et al.*,[7] the IMDC prognostic model which is similar to Motzer's or Heng's model, reliably discriminated the three risk groups to predict OS and time to treatment failure in NCC RCC although the differences were not statistically significant in our cohort due to small sample size.

The study is the first report on the treatment outcomes of NCC mRCC in India. Although most published studies have described the outcomes about a treatment agent or histological

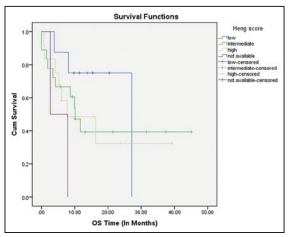

Figure 3: Kaplan–Meier graph showing median overall survival of nonclear cell metastatic renal cell carcinoma patients stratified as per Heng's risk stratification model

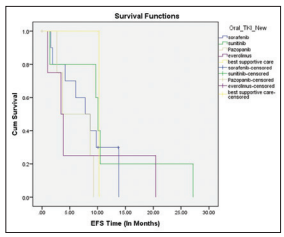

Figure 4: Kaplan–Meier graph showing median event-free survival of Papillary metastatic renal cell carcinoma patients stratified as per different first-line treatments

subtype, our study has a mixed cohort of different tumor types of different risk groups with different treatment agents. Although this study has its intrinsic limitations of being a retrospective study, constrained by a small sample size, short follow-up, inadequate data capture from medical records with patients lost to follow-up, incomplete response evaluation and no statistically significant results, it does reflect the outcome patterns of different targeted treatments and NCC subtypes to guide practice.

Conclusions

Our results in NCC mRCC correspond to the published literature. Chromophobe histology has better outcome followed by papillary subtype compared to other histological subtypes. Anti-VEGF TKIs are preferable first-line agents compared to everolimus overall. Among different TKIs– pazopanib seems to be superior to sunitinib, and a prospective comparative study is warranted in this line. In papillary mRCC, sunitinib has better results compared to sorafenib while pazopanib needs more clinical experience. Baseline risk grouping, the initial response to therapy and 2nd line therapy are important factors affecting the outcome in NCC mRCC.

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Conflicts of interest

There are no conflicts of interest.

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