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Utility of cytoreductive nephrectomy in targeted therapy era- retrospective analysis

Oncology

KEYWORDS: Renal cell carcinoma; metastatic; nephrectomy; TKIs

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ABSTRACT

Background: Metastatic RCC(mRCC) patients have poor prognosis with a 2-year survival of 10-20%. Prior trials of targeted agents for the treatment of mRCC had most of the patients undergone prior nephrectomy, hence the benefits of such agents can be recognised within the context of a resected primary only.

Objective: To analyse the additional benefit of cytoreductive nephrectomy to tyrosine kinase inhibitors(TKIs) in mRCC.

Design, setting, and participants: This is a single institutional retrospective study performed to address the survival benefit of CN in mRCC patients treated with targeted therapy over a period 2007 to 2014. All mRCC were categorised in two groups, First, patients received TKI after CN and Second, only TKI.

Outcome measurements and statistical analysis: Relationships with outcome analysed using Kaplan-Meier methods and log-rank analysis.

Results and limitations: We analysed 189 patients in our study, out of which 71 received only TKI therapy with a median follow up of 26.2 months. CN was done in 118 patients out of which 112 also received TKI therapy. Six -month PFS was 21% in TKI and 65% in CN group(p=0.0001). At the end of one year, all the patients TKI had progression while PFS in CN was 16.9%(p=0.0001). The median OS for CN patients was 16.4 months(95% CI, 7.2-34) versus 7.8 months(95% CI, 3.8-22.2) in TKI group(p=0.03). Limitations of this study were retrospective analysis, patient selection bias regarding performance status.

Conclusions: We concluded CN may provide an OS and PFS benefit in mRCC patients treated with targeted therapy.

INTRODUCTION

Renal cell carcinoma(RCC) is a common urogenital malignancy that comprises approximately 3.9% of new cancers with up to 25% of patients presenting with systemic metastasis.[1] Metastatic RCC(mRCC) patients have poor prognosis with a 2-year survival of 10-20%.[2] RCC is inherently resistant to cytotoxic therapy or radiation.[3] Over the past decade, systemic management of mRCC has underwent significant change with increased understanding of molecular biology of RCC. Targeted therapies have been designed to target pathways involved in RCC pathogenesis which have demonstrated impressive gains in overall survival(OS) and progression free survival(PFS) leading to replacement of immunotherapy as first line therapy.[4]

The cytoreductive nephrectomy(CN) combined with immuno therapy was considered as standard of care in mRCC before the development of targeted agents. The results of the European Organisation for Research and Treatment of Cancer(EORTC) -3047 and Southwest Oncology Group(SWOG)-8949 solidified the role of CN in immunotherapy era[5,6]. Because Tyrosine kinase inhibitors(TKIs) have a different mechanism of action than cytokine immunotherapies, it is questionable whether CN will improve the efficacy of TKI therapy. Also it is important to note that the clinical trials that led to the approval of targeted agents for the treatment of mRCC had most of the patients undergone prior nephrectomy, hence the benefits of such agents can be recognised within the context of a resected primary only.[Table1]. At present, it is not well understood whether CN should remain a part of the standard treatment protocol or not. This is a single institutional retrospective study performed to address the survival benefit of CN in mRCC patients treated with targeted therapy.

MATERIAL & METHODS

We reviewed the medical records of 816 RCC patients treated at our hospital from 2007 to 2014.We found 228 patients of mRCC from which we excluded the patients with Non-clear cell histology, ECOG≥2, venous thrombus level>1 of Nevus classification, received prior immunologic therapy, metachronus metastatic presentation and brain metastasis. One hundred eighty-nine patients were included in our study, out of which 71 received only TKI therapy. CN was done in 118 patients out of which 112 also received TKI therapy whereas 6 patients didn't receive any targeted therapy and were excluded from the analysis. The data regarding the patient characteristics, investigations, disease status, operative procedure and the use of targeted therapy was collected from the case record files. Patients were further divided into sub groups on the basis of No. of metastasis, site of metastasis & International Metastatic Renal Cell Carcinoma Database Consortium(IMDC) prognostic factors. Progression -free survival (PFS) was defined as the time interval between the initiation of targeted therapy and the date of progression or death. Overall survival (OS),was defined as the time interval between the initiation of targeted therapy and the date of death or last date of follow -up.

Statistical analysis

Target enrolment and events defined to provide at least 50% improvement in PFS (primary end point) and 50% improvement in OS (secondary end point). Efficacy end points were analysed in all

patients randomized to a treatment arm according to the intention-to-treat principle. Continuous variables analysed with use of Mann-Whitney U test and proportions were compared in Chi-square test. Kaplan-Meier methods were used to analyse PFS and OS. Comparisons between arms were made using a log-rank test. The value of p≤0.05 was considered statistically significant.

RESULTS

The 183 patients included in our study were divided in two groups-TKI group having 71 patients and CN group in which patients also received TKI having 112 patients.The median follow-up of all patients was 26.2 months(95% confidence interval (CI), 7.2-34).At the time of analysis, 68(96%) patients had died in TKI group while 92(82%) patients had died in CN with TKI group.

All patients received targeted therapy with Sunitinib being the common drug prescribed(75%).Baseline characteristics of patients in CN with TKI and TKI only group is shown in table 2.Patients undergoing CN compared to TKI only group had better IMDC prognostic profiles: 12.5% vs 5.7% good and 34% vs 40.8% poor. Patients having intermediate profile were similar in both groups (53.5%).Fewer CN patients had bone metastasis,liver metastasis and less number of metastatic site compared to TKI only group patients , however the difference was statistically insignificant.

The median OS for CN patients was 16.4 months(95% CI, 7.2-34) versus 7.8 months(95% CI, 3.8-22.2) in TKI group(p=0.03). CN was also associated with an increase in PFS. Six -month PFS was 21% in TKI and 65% in CN group(p=0.0001). At the end of one year, all the patients TKI had progression while PFS in CN was 16.9%(p=0.0001). Two-year OS was 4.2months in TKI while 17.8 months in CN group(p=0.0001).

Analysis of various sub-groups is shown in table 3 &4. Patients belonging to all the three IMDC prognostic profiles had their PFS and OS improved by CN but statistical significance was reached only for PFS in intermediate group(p<0.0001) and for both PFS and OS in poor group(p<0.0001,p<0.0001).Patients with single or two metastatic site derived statistical significant improvement in PFS and OS by CN while in patients having more than two metastatic site , result was insignificant. Patients with Pulmonary metastasis patients had their PFS and OS improved by CN which was statistically significant(p<0.001,p<0.0001) while bone metastasis patients had statistical improvement only in PFS(p=0.03).

DISCUSSION

Historically, cytokine immunotherapies such as high -dose interleukin-2(IL-2) and interferon(IFN)- α have been the cornerstone of mRCC treatment. Immunotherapy is based on the fact that RCC is immunogenic and IL-2 & INF-α are used to stimulate anti-tumor immune response.[15,16] The utility of CN in addition to immnunotherapy was well established by EORTC-3047 and SWOG-8949 trials. A combined analysis of the above SWOG and the EORTC trials by Flanigan et al. showed an overall survival of 13.6 months for nephrectomy plus INF-α vs. 7.8 months for INF-α alone.[17]

With the discovery of molecular pathways involved in the pathogenesis of RCC, various targeted therapies have been developed leading to approval of the vascular endothelial growth factor (VEGF) inhibitors sunitinib,sorafenib, pazopanib, bevacizumab and axitinib and the mammalian target of rapamycin(mTOR) inhibitors temsirolimus and everolimus. The benefits of targeted therapy over cytokine therapy include ease of administration, toxicity profile and superior efficacy in progression-free and overall survival.[18] Thus, targeted therapy has replaced cytokines as the dominant systemic therapy in mRCC.

Despite these advantages, the majority of evidence supporting the integration of surgery and systemic therapy is from the cytokine era and its role with newer targeted therapy has yet to be established. Furthermore, such advances in the treatment of metastatic RCC have led some investigators to question the benefit of CN. A recent Cochrane review highlights over 13 trials out of 28 that showed improved progression free survival with new targeted agents and that nephrectomy status did not appear to be essential to benefit from targeted therapy.[19] You et al. reported that CN provided no survival benefit in 78 patients with mRCC in receiving TKI therapy with or without nephrectomy despite the median OS in the CN group was twice that compared to the in the non-CN group (21.6 vs. 13.9 months).[20]

In contrast, Heng et al, in his retrospective study over 1658 mRCC patients from the IMDC showed that the median OS of patients with CN versus without CN was 20.6 versus 9.5 months (p< 0.0001).[21] A large study by Conti SL et al examining CN and survival in both the era of immunotherapy and targeted therapy noted an OS of 19 months for targeted therapy with CN versus only 4 months for targeted therapy alone.[22] Our study also showed benefit in OS for CN patients(16.4 months) versus in TKI group(7.8 months)(p=0.03).

Although nephrectomies are a fairly safe procedure, CNs carry a higher mortality rate, and they are associated with higher morbidity and in-hospital complications that may reduce quality of life during recovery compared with those without CN.[23] Careful patient selection is critical in determining if a patient will benefit from a CN because those with poor survival outcome or who are likely to progress rapidly may receive minimal benefit. Heng et al showed the improvement in OS with in intermediate and poor group of IMDC prognostic profiles(p<0.001,p<0.001)(3) which is similar to our result. Heng et al also showed better OS with CN in patients with metastatic sites 1 or more than 1(p<0.001)[21] but in our study the improved OS was limited to patients having metastatic site less than two.CN in pulmonary metastasis increased the OS but in case of bone metastasis only PFS was increased.

The optimal answer to whether CN will be of benefit in the era of targeted therapy may be fulfilled by the ongoing CARMENA phase III trial (NCT00930033) which is comparing nephrectomy plus sunitinib or sunitinib alone by recruiting 700 mRCC patients. However, this trial is not anticipated to report for some time and so the results of retrospective studies becomes important to guide us until then.

Limitations of our study included that it was retrospective and patients may be prone to selection bias. Our study is also limited in our ability to adjust for prognostic factors that are unknown or not collected because it is not possible to control for all factors, and we were unable to account for perioperative mortality or surgery-related morbidity.

Our study demonstrate that CN may provide an OS and PFS benefit in mRCC patients treated with targeted therapy and the benefit is derived irrespective of the patients IMDC prognostic profiles.

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Figure legends

Figure 1: Schematic presentation of study population
Figure 2: Kaplan-Meier Curve depicting the progression free survival
Figure 3: Kaplan-Meier Curve depicting the 2-year overall survival

Tables

Table 1: Cytoreductive nephrectomy in molecular targeted therapy trials

TRIALS	AGENT	PHASE	PATIENTS(n)	NEPHRECTOMY(%)
MOTZER et al 2007[7]	Sunitinib	III	375	91
ESCUDIER et al 2007[8]	Sorafenib	III	451	94
HUDES et al 2007[9]	Temsirolimus +/- IFN	III	419	67

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BUKOWSKI et al 2007[10]	Bevacizumab +/- Tarceva	II	104	100
YANG et al 2003[11]	Bevacizumab	II	76	90
ESCUDIER et al 2010[12]	Bevacizumab +/-IFN	III	327	100
STERNBERG et al 2010[13]	Pazopanib	III	258	89

Table 2-PATIENTS & DISEASE CHARACTERISTICS				
Variables		TKI, N=71	CN, N=112	p value
Age; median in years (range)		62.0(56-74)	59.0 (52-79)	0.91
Gender				0.75
	Male	52(73%)	79(71%)	
	Female	19(27%)	33(29%)	
IMDC prognostic criteria[14]				0.26
	Good	4(5.7)	14(12.5)	
	Intermediate	38(53.5)	60(53.5)	
	Poor	29(40.8)	38(34)	
Type of targeted therapy+				0.2
	Sunitinib	46(64.7)	92(82)	
	Sorafinib	18(25.3)	16(14)	
	Others	7(10)	4(4)	
Metastatic site				0.14
	Lung	46(64.7)	88(78.5)	
	Bone	34(48)	40(36)	
	Liver	15(21)	13(12)	
Number of Metastatic sites				0.09
	1	54(76)	89(79)	
	2	10(14)	18(16)	
	≥3	7(10)	5(5)	

+ - Sunitinib 50mg/day for first 4 weeks of 6 weeks cycle, Sorafenib 400mg twice daily, Others include-pazopanib, Temsirolimus, Everolimus, Axitinib ,Bevacizumab

Table 3: Progression free survival

VARIABLES		PFS				
		CN	TKI	p VALUE	SE	95%CI
GENDER						
	MALE	8.6±4.34	4.33±2.35	<0.001	0.658	2.96-5.57
	FEMALE	8.2±3.87	4.88±2.39	0.001	0.983	1.34-5.29
RISK CATEGORY+						
	GOOD	12.2±5.45	8.25±3.22	0.19	2.89	2.18-10.08
	INTERMEDIATE	9.17±3.83	5.10±2.35	<0.0001	0.69	2.69-5.44
	POOR	6.04±2.56	3.15±1.03	<0.0001	0.505	1.88-3.89
NUMBER OF METASTASIS						
	1	9.38±4.22	5.0±2.43	<0.0001	0.63	3.13-5.62
	2	6.11±2.29	3.2±0.71	0.006	0.749	1.37-4.44
	≥3	3.54±1.22	2.25±0.917	0.06	0.614	0.078-2.65
METASTATIC SITE						
	PULMONARY	9.9±4.48	4.89±2.49	<0.001	0.849	3.32-6.69
	BONE	7.14±2.05	5.56±2.38	0.03	0.719	3.03-10.12
	LIVER++		3.45±1.75			

+- Based on IMDC prognostic profiles ++- only one patient with liver metastasis

Table 4- Overall Survival

VARIABLES	OS					
		CN	TKI	P VALUE	SE	95%CI
GENDER						
	MALE	17.7±8.49	10.5±9.98	<0.001	1.62	3.98-10.41
	FEMALE	17.9±9.30	10.5±5.69	0.002	2.357	2.66-12.13
RISK CATEGORY+						
	GOOD	23.5±10.88	13.2±7.54	0.09	5.86	2.12-22.72
	INTERMEDIATE	19.8±8.16	12.8±11.22	0.81	1.71	2.99-3.79
	POOR	13.2±5.63	7.12±3.13	<0.0001	1.163	0.86-6.26
NUMBER OF METASTASIS						
	1	19.8±8.48	12.04±9.78	<0.0001	1.55	4.69-10.82
	2	11.3±3.77	6.47±1.62	0.007	1.26	2.24-7.41
	≥3	6.72±2.80	4.54±2.34	0.17	1.48	1.12-5.48
METASTATIC SITE						
	PULMONARY	21.3±8.78	11.38±7.77	0.0001	1.8116	6.315-13.52
	BONE	15.6±5.12	14.42±13.19	0.71	3.18	5.27-7.63
	LIVER++		6.55±1.68			

+- Based on IMDC prognostic profiles ++- only one patient with liver metastasis

Figure 1: Schema of the study

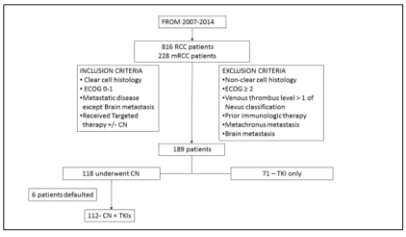


Figure 2: Kaplan -Meier curve depicting the PFS from the initiation of targeted therapy

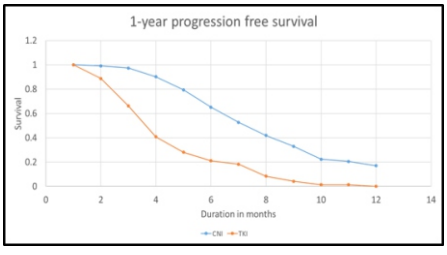
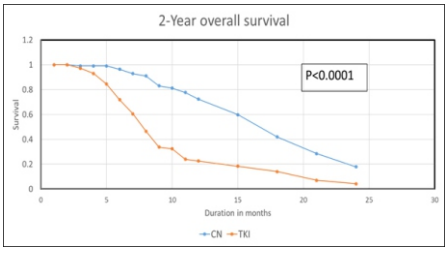


Figure 3: Kaplan-Meier curve depicting the overall survival from the initiation of targeted therapy



References

1. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J 2008;14:288-301.
2. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454-63.
3. Coppin C, Le L, Porzsolt F, et al. Targeted therapy for advanced renal cell carcinoma. Cochrane Database Syst Rev CD006017, 2008
4. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005;353:2477-90.
5. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–9.
6. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–70.
7. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516-24.
8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-34. Erratum in: N Engl J Med 2007;357:203.
9. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
10. Bukowski RM, Kabbinavar FF, Figlin RA, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. J Clin Oncol 2007;25:4536-41.
11. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427-34.
12. Escudier B, Bellmunt J, Négrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010;28:2144-50.
13. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.
14. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multi-center study. J Clin Oncol 2009;27:5794–9.
15. Fyfe G, Fisher RI, Rosenberg SA et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995;13:688–696.
16. Jonasch E, Haluska FG. Interferon in oncological practice: Review of interferon biology, clinical applications, and toxicities. Oncologist 2001; 6:34–55.
17. Flanigan RC, Mickisch G, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071-6.
18. Crispen PL, Blute ML. Role of cytoreductive nephrectomy in the era of targeted therapy for renal cell carcinoma. Curr Urol Rep 2012;13:38-46.
19. Coppin C, Kollmannsberger C, Le L, et al. Targeted therapy for advanced renal cell cancer (RCC): A Cochrane systematic review of published randomised trials. BJU Int 2011;108:1556-63.
20. You D, Jeong IG, Ahn JH, et al. The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy. J Urol 2011;185:54-9.
21. Heng DYC, Wells JC, Rini BI, et al. Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Euro Uro 2014;66:704 – 10.
22. Conti SL, Thomas IC, Hagedorn JC, et al. Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. Int J Cancer 2014;134:2245–52.
23. Abdollah F, Sun M, Thuret R, et al. Mortality and morbidity after cytoreductive nephrectomy for metastatic renal cell carcinoma: a population-based study. Ann Surg Oncol 2011;18:2988–96.