Efficacy of Targeted Treatment Beyond Third-Line Therapy in Metastatic Kidney Cancer: Retrospective Analysis From a Large-Volume Cancer Center

Sonia Vallet,[1] Sascha Pahernik,[2] Thomas Höfner,[5] Georgi Tosev,[2] Boris Hadaschik,[2] Stefan Duensing,[3] Oliver Sedlaczek,[4] Markus Hohenfellner,[2] Dirk Jäger,[1] Carsten Grüllich[1], for the Renal Cancer Center at the National Center for Tumor Diseases (NCT) Heidelberg, Germany

Abstract

We retrospectively analyzed the outcome of patients with metastatic kidney cancer beyond third-line treatment. Median overall survival from first-line therapy exceeded 5 years and from initiation of fourth line was above 30 months. Median progression-free survival from fourth-line treatment was 5.8 months. Poor response to first-line treatment did not preclude patients from achieving objective response and survival benefit in advanced lines.

Introduction/Background: Currently, 7 agents are approved for the first- and second-line therapy for metastatic renal cell carcinoma. In contrast, data supporting their use beyond second line are limited. Here we summarize our experience in patients treated with more than 4 lines of therapy. **Methods:** We retrospectively assessed the outcome of 24 patients treated at our institution with at least 4 lines of therapy. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier estimates. **Results:** Median OS from the initiation of first-line therapy for the whole cohort is 64.7 months. Up to 96% of the patients received a tyrosine kinase inhibitor (TKI) and mammalian target of rapamycin (mTOR) inhibitor (mTOR-I) within the first 3 lines of treatment. In the fourth or following lines, patients were treated with TKI, mTOR-I, bevacizumab/interferon, or experimental drugs. Seven patients continued treatment with a sixth-line agent; one has been treated up to the ninth line. Sixteen percent of the patients receiving fourth-line therapy and 13% receiving fifth-line therapy experienced a partial remission, which was independent from response to previous therapies. Median OS from fourth and fifth line was 30.8 and 26.2 months, respectively. Median PFS for fourth-line therapy was 5.8 months. No significant difference in PFS was observed for patients with disease that responded or did not respond to first-line therapy. **Conclusion:** Despite the limitations of a retrospective analysis, our study suggests that selected patients benefit from multiple lines of treatment, independent of response to first-line therapy. However, the optimal sequence of treatment with regard to later lines remains to be determined.

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Introduction

With more than 60,000 estimated new cases for 2014, kidney cancer represents the sixth most common malignant neoplasia in the United States.[1] About one-third of the patients experience metastatic disease, which confers a poor prognosis. Overall survival (OS) ranges from 7% to 75% at 2 years.[2]

[1]Department of Medical Oncology, National Center for Tumor Diseases Heidelberg
[2]Department of Urology
[3]Department of Urology, Section of Molecular Urooncology
[4]Department of Radiology
Heidelberg University Hospital, Heidelberg, Germany
[5]Department of Urology, Theresienkrankenhaus, and St. Hedwig-Klinik GmbH, Mannheim, Germany

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Address for correspondence: Carsten Grüllich, Department of Medical Oncology, National Center for Tumor Diseases (NCT) Heidelberg, University Hospital Heidelberg, Im Neuenheimer Feld 460 and 110, 69120 Heidelberg, Germany
Fax: + 49 06221 56-5315; e-mail contact: carsten.gruellich@med.uni-heidelberg.de

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Table 1 Patient Characteristics

Characteristic	Diagnosis	Line of Therapy		
		First	Fourth	Fifth
No. of patients	24	24	24	15
Age, median (range)	57 (35-69)	59 (37-74)	63 (39-76)	64 (39-75)
Gender, M/F ratio	21/3	21/3	21/3	12/3
Histology, clear cell/papillary	20/4	20/4		
Nephrectomy	24	24		
ECOG 0-1/2-3	24/0	24/0		
MSKCC risk score, favorable/intermediate/poor		12/12/0		
Metastatic disease at diagnosis	10			
Metastatic Site at Diagnosis				
Visceral	10			
Bone	6			
Lymph nodes	2			
Multiple sites	9			
Time to initiation of systemic therapy, months, median (range)		10.5 (0-199)		
Treatment discontinuation due to toxicity		4	0	1

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan Kettering Cancer Center.

Since the approval of the first targeted therapy, sorafenib, in 2005, the therapeutic landscape has dramatically changed, and patient outcome has significantly improved. Survival in metastatic renal cell carcinoma (mRCC) significantly increased from about 9 months in the immunotherapy era (2002 to 2005) to 26 months in the targeted era.[3]

Targeted agents include tyrosine kinase inhibitor (TKI), inhibitors of the mammalian target of rapamycin (mTOR) pathway (mTOR-I), and the anti–vascular endothelial growth factor antibody bevacizumab. They mainly target tumor neoangiogenesis, leading more frequently to disease stabilization than objective tumor responses. The efficacy of these agents appears to be the greatest in the first-line setting, with the choice of agent class being important for OS.[4] Second-line treatment after targeted therapy is much less beneficial, with only small gains in progression-free survival (PFS) and without demonstration of an OS advantage.[5] The optimal sequencing of targeted therapy is still unclear as a result of the lack of biomarkers driving patient selection.[6,7]

The most prevalent histology in mRCC is clear cell carcinoma (approximately 80%), and clinical trials preferentially enrolled patients with this subtype. However, available data suggest that targeted agents are also active in non–clear-cell carcinoma except for the sarcomatoid subtype, but with an inferior clinical benefit compared to clear cell histology.[8]

Currently, 7 different agents are approved for first- and second-line therapy.[5,9-13] Third-line treatment is often offered within clinical trials or as compassionate use, and therapeutic choices are mainly supported by observational studies and case-series.[5,9,14,15] Despite the lack of evidence, treatment beyond the third line is increasingly incorporated into clinical practice in selected patients. Because prospective clinical trials are not available and will not be in the near future, only retrospective data may help identify patients for whom a rationale for treatment beyond the third line might exist.

In this retrospective analysis, we report on 24 patients receiving treatment beyond the third line at our institution. To our

Table 2 Treatment Characteristics

Line of Therapy	Immunochemotherapy			TKI			mTOR-I			Bev/IFN			Experimental Agents		
	n (%)	OR	PFS	n (%)	OR	PFS	n (%)	OR	PFS	n (%)	OR	PFS	n (%)	OR	PFS
First	6 (25)	0	3	15 (62)	7	9.9	3 (12)	0	12.9	0			0		
Second	0			19 (79)	6	5	5 (20)	0	3.9	0			0		
Third	0			13 (54)	4	6.2	8 (33)	1	2	1 (4)	0	3	2 (8)	1	6.9
Fourth	0			12 (50)	4	5.9	9 (37)	0	7.9	2 (8)	0	1.4	1 (4)	0	2
Fifth	0			6 (40)	2	7.7	2 (13)	0	2.9	5 (33)	0	26.2	2 (13)	0	1.4

Abbreviations: Bev/IFN = bevacizumab/interferon; mTOR-I = mTOR inhibitor; OR = objective responses (partial + complete remission); PFS = median progression-free survival in months; TKI = tyrosin kinase inhibitor.