Original Study

Synergistic Survival: A New Phenomenon Connected to Adverse Events of First-Line Sunitinib Treatment in Advanced Renal Cell Carcinoma

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Abstract

Significantly longer survivals were observed when some adverse events occurred after first-line sunitinib treatment of 274 patients with advanced renal cell carcinoma. The higher number of adverse events was an independent marker of longer progression-free and overall survival. Multiple adverse events increased progression-free and overall survival in a synergistic manner.

Background: The aim was to assess the relationship between treatment efficacy and adverse events (AEs) for patients with advanced renal cell carcinoma treated with first-line sunitinib. **Patients and Methods:** 274 patients were treated with sunitinib (50 mg/d, 4-weeks-on and 2-weeks-off schedule). Physical and laboratory evaluations were done every sixth week. AEs were diagnosed at every visit. Clinical response was assessed every 3 months. The objective response rate (ORR), median progression-free (mPFS) and median overall survival (mOS) and AEs were evaluated. Besides χ^2 and log rank tests, multivariate Cox regression analysis and for synergism 1-sided *t* tests were used. **Results:** The ORR was 25%. After a median follow-up of 32 months, the mPFS and mOS were 9 and 19 months, respectively. Hypertension, diarrhea, hypothyroidism, mucositis, hand-foot syndrome (HFS), skin toxicity, and leukopenia were the most frequent treatment-associated AEs. Significantly longer ($P < .01$) mPFS and mOS were observed when hypertension, diarrhea, HFS, hypothyroidism, skin toxicity, or leukopenia occurred. A statistically significant synergistic effect of the listed AEs was observed for progression-free survival ($P < .001$) and overall survival ($P < .001$). Multivariate analysis revealed that besides the prognostic category, the higher number of AEs (3-6 vs. 0-2) was an independent marker of longer mPFS (24 vs. 5 months, respectively; $P < .001$) and mOS (51 vs. 9 months, respectively; $P < .001$). **Conclusion:** Results of this study provide evidence for the synergistically enhanced efficacy of sunitinib treatment in patients who present multiple AEs. These AEs are diagnosed routinely and their coexistence can help physicians to predict which group of patients would benefit the most from first-line sunitinib treatment.

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Introduction

Renal cell carcinoma (RCC), which originates from within the renal cortex, constitutes 80% to 90% of primary renal neoplasms. Among RCC, clear cell RCC (70%-80%) is the most common histological subtype.[1] RCC is the most lethal urological malignancy and the incidence is currently increasing in Europe (doubled in the past 30 years).[2] Globally, the incidence of RCC varies widely in a region-specific manner with the highest rates observed in Europe and North America.[3] In 2010 in Hungary, 1173 new female and 1562 new male cases of RCC were registered and 818 patients died of the disease.[4]

Unfortunately, one-third of the patients exhibit visceral metastasis at the time of initial diagnosis, and up to half of them develop distant metastasis. For metastatic RCC (mRCC), the possibilities for treatment were limited until 2005, with immunotherapy being

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Table 1 Clinicopathological Characteristics and Response of Patients With Advanced RCC Treated With First-Line Sunitinib

Parameter	n	(%)
Gender		
Male	192	70
Female	82	30
Age		
Mean (Range)	62 (32-90)	
≤65 years	157	57
>65 years	117	43
Histopathology		
Clear-cell RCC	230	84
With other components	44	16
Metastasized organs, n		
1	106	39
2	90	33
3	54	20
4	16	6
≥5	8	3
Disease Localization[a]		
Lung	181	66
Lymph node, regional	90	33
Lymph node, distant	57	21
Suprarenal gland	49	18
Liver	46	17
Bone	44	16
Local recurrence	26	9
Contralateral adrenal gland	20	7
Brain	16	6
Other[b]	15	5
Prognostic Category		
Good	74	27
Intermediate	200	73
Nephrectomy		
Yes	237	86
No	37	14
Best Clinical Response		
CR	12	4
PR	57	21
SD	121	44
PD	84	31
Objective response (CR + PR)	69	25
Clinical benefit (CR + PR + SD)	190	69
Deaths	159	58
Discontinued Because of Toxicity	25	9
Still on Treatment	65	24
Metastasectomy	10	4
Second-Line Treatment		
Everolimus	44	16
Other[c]	28	10

Abbreviation: RCC = renal cell carcinoma.
[a]Includes patients with more than 1 site of recurrence.
[b]Skin (n = 7), pancreas (n = 4), thyroid gland (n = 2), sinus maxillaris (n = 1), spleen (n = 1).
[c]Sorafenib, temsirolimus, axitinib, radiochemotherapy.

the standard treatment with a median overall survival (mOS) of approximately 12 months and relatively high toxicity.[2,5]

Better understanding of the underlying molecular biology of RCC has led to the identification of the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and mammalian target of rapamycin signaling pathways as important mediators of tumor cell growth.[1] The orally available drug, sunitinib, is a targeted inhibitor of multiple tyrosine kinases, including VEGF receptors and PDGF. It was approved by the US Food and Drug Administration for the treatment of RCC on January 26, 2006. Currently, sunitinib remains the gold standard of care in the treatment of mRCC.[2] Motzer et al proved that monotherapy with interferon-α was inferior to sunitinib in patients with advanced or mRCC classified as Memorial Sloan Kettering Cancer Center (MSKCC) good- and intermediate-risk.[6] In Hungary sunitinib was first available in 2005 in clinical trials. In 2010 it became available in the first-line setting and it is currently a standard initial treatment for patients classified in MSKCC good or intermediate prognostic groups of advanced RCC.

Targeted biological agents are not exempt from adverse events (AEs). Side effects not primarily related to the inhibition of VEGF signaling (off-target AEs) include fatigue or asthenia, diarrhea, skin rash, stomatitis or mucositis, hand-foot syndrome (HFS), cardiotoxicity, and hematological and liver toxicity. Direct VEGF inhibition-related on-target AEs include hypertension (HTN), bleeding, thromboembolic events, hypothyroidism, ulceration, and renal and pancreatic toxicity.[2,7]

Previous studies showed that some of these AEs have predictive value for the efficacy of sunitinib treatment.[8-10] The aim of this retrospective study was to systematically analyze the relationship between treatment efficacy and AEs, including the correlations with on- or off-target and the total number of AEs with treatment outcome.

Patients and Methods

Between November 2005 and April 2014 a total of 448 patients with advanced RCC were treated with sunitinib at the uro-oncological department. Of this number, 274 patients were treated in the first-line setting.

A systematic retrospective analysis was performed to evaluate prognostic values of the AEs that most frequently occurred on treatment efficacy. Efficacy and toxicity data were collected from our institute's database. Clinicopathological examinations, performance