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Chapter 2

Signaling Pathways and Biomarkers in Renal Tumors

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Additional information is available at the end of the chapter

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1. Introduction

Sunitinib malate (Sutent, Pfizer inc., New York, NY) is an orally administered, multitargeted inhibitor of tyrosine kinases, including vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, stem cell factor receptor (KIT), fms-like tyrosine kinase (FLT) -3, CSF-1R, and RET. Since the introduction of sunitinib for patients with advanced renal tumor [1], significant objective responses of sunitnib have been revealed [2-6]. In a randomized, multicenter, phase III trial enrolled 750 patients with previously-untreated metastatic renal tumor to receive either sunitinib or interferon (IFN) -α, sunitinib was superior to IFN-α in the objective response rate (47% *vs* 12%), progression-free survival time (11.0 *vs* 5.0 months), and overall survival time (26.4 *vs* 21.8 months) [3, 4]. Also in a Japanese, multicenter, phase II trial enrolled 51 patients with first-line and pretreated metastatic clear-cell renal tumor to recieve sinitinib, significant responses of sunitinib have been reported that objective response rate was 52.9%, the median progression-free survival time was 12.2 and 10.6 months, and the median overall survival time was 33.1 and 32.5 months in first-line and pretreated patients, respectively [5, 6]. Sunitinib is approved worldwide for first-line treatment of advanced clear-cell renal tumor. However, approximately half of patients with advanced renal tumor do not see clinical benefits from sunitinib treatment. A prognostic marker is needed for selecting patients who will benefit most from sunitinib.

It has been advocated that the necessity of determining molecular and clinical biomarkers that may predict efficacy of sunitinib. The identification of biomarkers to predict response is urgently needed. This chapter provides a brief overview of the signaling pathways of renal tumors and introduces biomarkers to predict response to sunitinib of clinical variables.

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2. Signaling pathways in renal tumors

Renal tumors originates from the tubular structures of the kidney and is calssified into four major histological cell types. Clear-cell renal tumor is the most common type, accounting for approximately 75% of all renal tumors. Other types are followed by papillary renal tumor (approximately 15%), chromophobe renal tumor (approximately 5%), and renal oncocytoma (approximately 5%) [7].

The most important molecular disorder in renal tumors involves the von Hippel-Lindau (VHL) tumor suppressor gene, which is responsible for clear-cell renal tumors. The protein production of the *VHL* gene, which is located on chromosome 3p25, prevents angiogenesis and suppresses tumors [7]. Inactivating the phosphorylated VHL protein activates hypoxia-inducible factor (HIF) and the induction of VEGF in clear-cell renal tumors. Mesenchymal-epithelial transition factor (MET) and fumarate hydratase (FH) are responsible for papillary renal tumors. While chromophobe renal tumors, Birt-Hogg-Dube (BHD) tumor suppresor gene is mutated [8]. The inherited renal tumor genes *VHL*, *MET*, *FH*, *folliculin*, *succinate dehydrogenase*, tuberous sclerosis complex (TSC) 1, and *TSC2* are all involved in metabolic pathways related to oxygen, iron, energy, and nutrient sensing [9].

Alterations in proto-oncogenes and tumor suppressor genes leads to dysregulated signal transduction that underlies the abnormal growth and proliferation of cancer cells. Signaling proteins that are centrally located in important cancer-associated signaling networks can serve as therapeutic targets [10].

2.1. Angiogenetic signaling pathways

Renal tumors are frequnently characterized by hypoxic conditions. Hypoxia and compensatory hyperactivation of angiogenesis are thought to be particularly important in renal tumors, given the highly vascularized nature and the specific association of mutation in *VHL*, a critical regulator of the hypoxic response. Hypoxic signaling is mediated by HIF. Increased expression of HIF target genes is implicated in promoting cancer, inducing both changes within the tumor and changes in the growth of adjacent endothelial cells to promote blood vessel growth. The expression level of VEGF in renal tumors is known to strongly correlate with microvessel density [10].

2.2. PI3K/AKT/mTOR pathway

Mammalian target of rapamycin (mTOR) and protein kinase B (AKT) are key oncogenic process including cell proliferation, survival, and angiogenesis. PI3K promotes the generation of phosphatidylinositol-3, 4, 5-triphosphate. Signaling from VEGF and PDGF through AKT activates mTOR. Components of this PI3K/AKT/mTOR pathway are constitutively activated in renal tumors compared to normal renal tissues [11].

2.3. HGF/MET pathway

Changes in expression and activity of hepatocyte growth factor (HGF) and its receptor c-MET have been associated with renal tumors. HGF binding to MET leads to phosphorylation of two tyrosine residues at the C-terminus of MET, which leads to the recruitment of adapter proteins and activation of PI3K/AKT pathway to promote renal tumor growth and metastasis [12].

3. Biomarkers of response to sunitinib in renal tumors

3.1. Prognostic model

In the cytokine era, Motzer et al. [13] reported Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification, which is based on data from 463 patients with advanced renal tumor who were treated with IFN-α cytokine therapy as first-line systemic therapy. The MSKCC risk classification extracted five variable risk factors for short survival: low Karnofsky performance status (PS) (< 80%), high lactate dehydrogenase (> 1.5 times the upper limit of normal), low serum hemoglobin, high corrected serum calcium (> 10 mg/dL), and time from initial renal tumor diagnosis to IFN-α therapy of less than one year. Each patient was assigned to one of three risk groups: those with zero risk factors (favorable risk), those with one or two risk factors (intermediate risk), and those with three or more risk factors (poor risk). The median time to death was 30, 14, and 5 months in the favorable, intermediate, and poor-risk groups, respectively [13]. These five risk criteria are now most frequently used prognostic model for patients with advanced renal tumor.

In the era of targeted therapy, Heng et al. [14] reported a new prognostic model that added platelet and neutrophil counts to the MSKCC model from a large multicenter study of 645 patients with metastatic renal tumor who were treated with targeted therapy. This study included three groups of patients: 396 patients treated with sunitinib, 200 patients treated with sorafenib, and 49 patients treated with bevacizumab. Four of the five adverse prognostic factors according to the MSKCC risk classification–low hemoglobin, high corrected serum calcium, low Karnofsky PS, and time from the initial renal tumor diagnosis to the start of treatment of less than one year–emerged as independent predictors of poor survival. Additionally, platelets greater than the upper limit of normal range, and neutrophils greater than the upper limit of normal range, emerged as independent adverse prognostic factors. MSKCC model with the addition of platelet and neutrophil counts can be incorporated into patient care of targeted therapies [14].

3.2. C-reactive protein

C-reactive protein (CRP), a non-specific inflammatory acute-phase protein, is a representative marker of systemic inflammatory response. CRP levels correlate with the production of proinflammatory cytokines, such as interleukin (IL) -6 [15], and with tumor progression [16, 17]. It has been recognized as an important prognostic marker in the cytokine era. Atzpo-

dien et al. [16] reported data from 425 patients who received cytokine-based home therapy. On multivariate analysis, elevated CRP (≥ 1.1 mg/dL) was a poor prognostic factor, and Kaplan-Meier analysis demonstrated that patients with elevated CRP had significantly worse overall survival [16]. Casamassima et al. [17] reported that normal CRP (≤ 0.8 mg/dL) was the most independent prognostic factor for 110 patients treated with IL-2-based immunotherapy. Ramsey et al. [18] investigated the Glasgow Prognostic Score, which is based on a combination of hypoalbuminemia and elevated CRP (> 1.0 mg/dL). They found that CRP was independently associated with cancer-specific survival in 119 patients receiving immunotherapy [18]. Saito et al. [19] described that CRP kinetics have an impact on survival in patients with metastatic renal tumor treated with immunotherapy and/or metastasectomy. A decrease of CRP level during treatment predicts better prognosis in patients with metastatic renal tumor, and prolonged normalized CRP period is associated with prolonged survival [19].

Variable	Univariate		Multivariate	
	Odds Ratio (95% Confidence Interval)	*P*-value	Odds Ratio (95% Confidence Interval)	*P*-value
Pretreatment				
Age	0.988 (0.920–1.061)	0.7410		
Gender	0.573 (0.139–2.355)	0.4384		
ECOG PS0	4.200 (0.884–19.947)	0.0598		
MSKCC non-poor	0.150 (0.026–0.864)	0.0206	0.632 (0.058–6.850)	0.7042
First-line	0.879 (0.238–3.249)	0.8468		
Normal CRP	17.600 (1.961–157.970)	0.0011	13.525 (1.111–164.602)	0.0163
Adverse events				
Hypertension	3.667 (0.954–14.094)	0.0523		
HFS	6.500 (1.537–27.490)	0.0069	2.272 (0.324–15.930)	0.4104
Stomatitis	3.200 (0.826–12.404)	0.0844		
Diarrhea	1.375 (0.368–5.136)	0.6347		
Altered taste	8.250 (1.498–45.436)	0.0064	4.422 (0.533–36.655)	0.1517
Fatigue	5.133 (1.131–23.303)	0.0238	1.572 (0.192–12.841)	0.6740
Leukopenia	8.333 (0.867–80.130)	0.0337	5.436 (0.190–155.246)	0.2717
Anemia	1.771 (0.392–8.003)	0.4559		
Thrombocytopenia	758.701 (0.000)	0.0670		
Increased creatinine	2.182 (0.566–8.415)	0.2505		
TSH abnormalities	2.812 (0.734–10.774)	0.1255		

Table 1. Univariate and multivariate logistic regression analyses for selected variables

In the targeted therapy era, Fujita et al. [20] recently reported that CRP is an independent prognostic indicator for patients with advanced renal tumor treated with sunitinib. A total of

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41 consecutive patients between December 2008 and August 2011 were enrolled in this study. All patients had histologically proven clear-cell renal tumor. Non-tumor variables which were selected from pretreatment characteristics and treatment-related adverse events were analyzed on univariate and multivariate logistic regression analysis. Pretreatment characteristics were age, gender, Eastern Cooperative Oncology Group (ECOG) PS 0, MSKCC non-poor (favorable and intermediate) risk, first-line treatment, and normal CRP. Treatment-related adverse events were hypertension, hand-foot skin reaction (HFS), stomatitis, diarrhea, altered taste, fatigue, leukopenia, anemia, thrombocytopenia, increased creatinine, and thyroid-stimulating hormone (TSH) abnormalities. On univariate analyses among pretreatment characteristics, MSKCC non-poor risk classification and normal CRP level were significantly correlated with response to treatment (P = 0.0206 and 0.0011, respectively). Among adverse events, HFS, altered taste, fatigue, and leukopenia were significantly corralated with response to treatment (P = 0.0069, 0.0064, 0.0238, and 0.0337, respectively). Variable values in the multivariate analysis included MSKCC non-poor risk classification, normal CRP, HFS, altered taste, fatigue, and leukopenia. After adjusting for differences in these variables, normal CRP was independently associated with response to treatment (P = 0.0163).

Patients were grouped into two cohorts: those with normal CRP levels (≤ 0.30 mg/dL) and those with elevated CRP levels (> 0.30 mg/dL), according to the normal values provided by the manufacturer. The cohort with normal CRP comprised 10 males and 3 females (total 13 patients; 31.7%) with a median age of 63 years (range 46–77 years). The elevated CRP cohort comprised 20 males and 8 females (total 28 patients; 68.3%) with a median age of 64 years (range 36–80 years). MSKCC risk classification was favorable for 15.4% of the normal CRP cohort and intermediate for 86.4%. In contrast, in the elevated CRP cohort, MSKCC risk classification was favorable for 21.4%, intermediate for 46.4%, and poor for 32.2%. The difference in risk classification between the two groups was statistically significant (P = 0.0377). There were no statistically significant differences in any other pretreatment variables and tumor characteristics. The rate of partial response plus stable disease to treatment was 84.6% for the normal CRP cohort and 35.7% for the elevated CRP cohort. The higher response rate observed in the normal CRP cohort was statistically significant (P = 0.0022).

	Normal CRP (≤ 0.30 mg/dL)	**Elevated CRP (> 0.30 mg/dL)**	***P*-value**
	13 (31.7%)	28 (68.3%)	
Gender (*n* (%))			0.7118
Male	10 (76.9)	20 (71.4)	
Female	3 (23.1)	8 (28.6)	
Age (years)			0.5953
Median	63	64	
Range	46–77	36–80	
Mean ± standard deviation	64.8 ± 9.0	63.2 ± 9.1	

	Normal CRP (≤ 0.30 mg/dL)	**Elevated CRP (> 0.30 mg/dL)**	***P*-value**
ECOG PS (*n* (%))			0.0595
0	12 (92.3)	18 (64.3)	
≥ 1	1 (7.7)	10 (35.7)	
MSKCC risk classification (*n* (%))			0.0377
Favorable	2 (15.4)	6 (21.4)	
Intermediate	11 (84.6)	13 (46.4)	
Poor	0 (0)	9 (32.2)	
Prior nephrectomy (*n* (%))			0.2767
Yes	12 (92.3)	22 (78.6)	
No	1 (7.7)	6 (21.4)	
T stage (*n* (%))			0.8187
T1 or T2	6 (46.2)	14 (50.0)	
≥ T3	7 (53.8)	14 (50.0)	
Grade (*n* (%))			0.6628
1 or 2	9 (69.2)	17 (60.7)	
3	3 (23.1)	8 (28.6)	
Prior immunotherapy (*n*)			0.2482
IFN-α	9	14	
IL-2 and IFN-α	3	6	
Prior targeted therapy (*n*)			0.8651
Sorafenib	5	10	
Metastatic sites (*n*)			
Lung	12	21	
Bone	2	12	
Lymph nodes	3	7	
Brain	1	3	
Pancreas	–	4	
Adrenal	–	4	
Skin	–	3	
Kidney	–	2	
Local	–	2	
Liver	–	2	

	Normal CRP (≤ 0.30 mg/dL)	Elevated CRP (> 0.30 mg/dL)	*P*-value
Prostate	1	–	
No. metastatic sites (*n* (%))			0.1929
1	6 (46.1)	8 (28.6)	
≥ 2	6 (46.1)	20 (71.4)	
Treatment (*n* (%))			0.2122
First-line	3 (23.1)	13 (46.4)	
Second-line	6 (46.1)	6 (21.4)	
Third-line	4 (30.8)	9 (32.2)	
Responses (*n* (%))			0.0022
Partial response plus stable disease	11 (84.6)	10 (35.7)	

Table 2. Patient characteristics grouped by CRP level

The median progression-free survival time for the elevated CRP cohort was 6.0 months. In contrast, the median progression-free survival time for the normal CRP cohort was significantly longer, at 19.0 months (log-rank $P = 0.0361$).

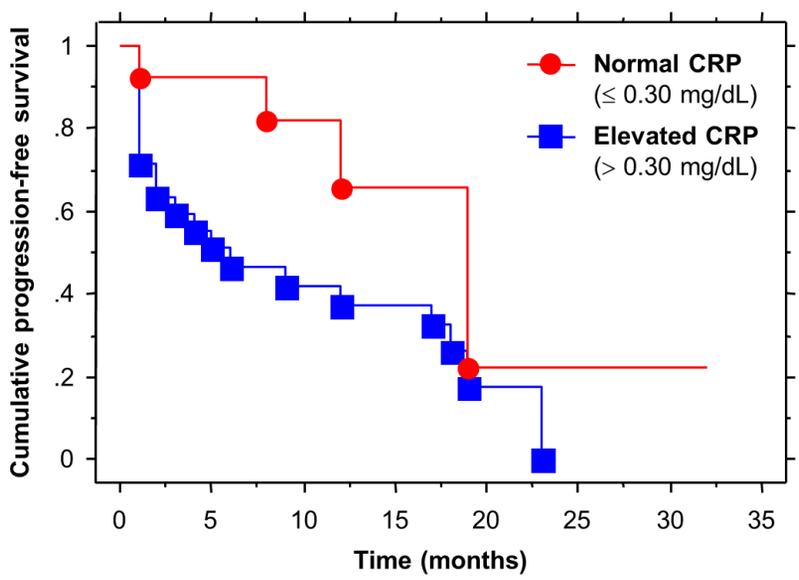


Figure 1. Kaplan-Meier progression-free survival for patients grouped by CRP level

CRP is a significant independent prognostic indicator for patients with advanced renal tumor treated with sunitinib. Pretreatment CRP level could be a useful biomarker for response to sunitinib treatment [20].

3.3. Selected adverse events

Sunitinib has been related a variety of adverse events, key notable clinical adverse events included diarrhea (61%), fatigue (54%), hypertension (30%), stomatitis (30%), HFS (29%), and asthenia (20%) [4]. Laboratory abnormalities also found that included leukopenia (78%), anemia (79%), increased creatinine (70%), and thrombocytopenia (68%) [4]. If adverse events depends on the degree of systemic exposure to sunitinib, on which clinical efficacy also depends, adverse events might be potential predictors of sunitinib efficacy [21]. Several authors have described the correlation between sunitinib responses and selected treatment-related adverse events.

3.3.1. Hypertension

Hypertension is commonly associated with targeted therapy. It develops when VEGF stimulates production of nitric oxide and prostacyclins in vascular endothelial cells [22, 23], vasodilatory mechanisms become inhibited, and peripheral vascular resistance increases, leading to increased blood pressure.

Rini et al. [24] demonstrated that sunitinib-associated hypertension is associated with improved clinical outcomes without clinically significant increases in hypertension-associated adverse events. This analysis included large pooled data from four clinical trilas of 4915 patients with metastatic renal tumor who were treated with sunitinib. Sunitinib-induced hypertension had significantly better outcomes than those without treatment-induced hypertension in the objective response rate (54.8% *vs* 8.7%), the median progression-free survival time (12.5 *vs* 2.5 months), and the median overall survival time (30.9 *vs* 7.2 months, $P< 0.001$ for all) [24].

Bono et al. [25] reported that sunitinib-induced hypertension was associated with frequent tumor response ($P = 0.001$), significantly longer disease progression time ($P = 0.0003$), and overall survival time ($P = 0.001$). On multivariate analysis including the variables of pretreatment hemoglobin, pretreatment calcium level, PS, time from diagnosis to onset of metastasis, and treatment-related hypertension, hypertension was an independent predictor of progression-free survival ($P = 0.0030$) [25].

Szmit et al. [26] reported that patients who developed hypertension related to sunitinib treatment experienced significantly longer progression-free survival time and overall survival time compared to those who did not hypertension ($P< 0.00001$). Patients treated with at least 3 antihypertensive agents experienced significantly longer progression-free survival time ($P = 0.00002$) and overall survival time ($P = 0.00001$) compared either with patients who received one or two medications or with patients who received no medications [26].

Rixe et al. [27] reported that appearance or worsening hypertension was found to be the single independent predictor of a better clinical response to sunitinib on multivariate analysis

using logistic regression model (P = 0.009). Furthermore, grade 3 hypertension was correlated with a better outcome (P = 0.03). The appearance of hypertension, particularly grade 3, was associated with higher treatment response to sunitinib in metastatic renal tumors. Early and intensive antihypertensive therapy with the goal of maintaining the sunitinib use may improve response rate in those patients [27].

Overall, hypertension related to sunitinib was a positive predictive factor associated with significantly better objective response rate, longer progression-free survival and overall survival in patients with metastatic renal tumor treated with sunitinib.

3.3.2. Hypothyroidism

Treatment-related hypothyroidism has been reported a useful predictor of progression-free survival for metastatic renal tumors undergoing treatment with sunitinib [28]. In the 52 patients with metastatic renal tumor treated with sunitinib, 13 patients (25.0%) developed hypothyroidism during treatment. Subclinical hypothyroidism was defined as serum TSH above the upper limit of normal, with total triiodothyronine (T3) and thyroxine (T4) within normal limits. Clinical hypothyroidism was defined as low serum T3 and T4 together with elevated TSH. Hypothyroidism was associated with a longer progression-free survival time (P = 0.032). Hormone replacement with 1-thyroxine did not have an influence on survival [28].

3.4. Others

Han et al. [29] reported the initial tumor enhancement on contrast-enhanced computed tomography (CT) could be useful as a clinical predictor during targeted therapy in 198 metastatic lesions of 46 patients. On multivariate analyses, tumor enhancement and enhancement pattern were associated with objective responses (P = 0.003 and 0.028, respectively). Additionally, tumor enhancement was associated with tumor size reduction (P = 0.004). On Cox proportional hazards models, only tumor enhancement was associated significantly with the time to size reduction and progression-free survival time (P = 0.03 and 0.015, respectively). Tumor enhancement on contrast-enhanced CT was associated with tumor size reduction, time to response, and time to progression of individual metastases in patients with metastatic renal tumor who received targeted therapy [29].

Kayani et al [30] revealed prognostic significance of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT as a biomarker of response to sunitinib. A total of 44 patients with newly diagnosed untreated metastatic renal tumor were enrolled in this study. ^{18}F-FDG-PET/CT scans were conducted before, after 4 weeks, and after 16 weeks of sunitinib given. On multivariate analysis, a high SUV_{max} and an increased number of PET-positive lesions correlated with shorter overall survival. The early metabolic responses are associated with a pharmacodynamic effect of drug and it is not until later identification with acquired resistance occurs [30].

Yuasa et al. [31] reported that initial tumor size is inversely associated with the tumor reduction rate of individual metastatic sites and primary tumors in patients with metastatic renal tumor who underwent targeted therapy. A data from 139 metastatic and 16 primary lesions

treated with targeted agents were analyzed. Both univariate and multivariate linear regression analyses revealed that only the initial tumor size was associated with the rate of reduction in individual tumors ($P< 0.001$) [31].

Abel et al. [32] reported that early 10% decrease in tumor diameter of the primary tumor was predictive of improved overall survival in patients with metastatic renal tumor treated with sunitinib. In 75 consecutive treatment-naive patients, median overall survival time for patients without minor primary tumor response, with minor primary tumor response after 60 days, and with early minor primary tumor response was 10.3, 16.5, and 30.2 months, respectively. On multivariate analysis, early minor response was an independent predictor of improved overall survival ($P = 0.031$) [32].

High visceral fat area could be a predictive biomarker from shorter survival in patients given first-line antiangiogenic agents including sunitinib for metastatic renal tumors [33]. In 113 study population, 46 patients received sunitinib as first-line therapy. Visceral fat area was measured retrospectively on the available CT scans performed before sunitinib initiation at the level of the umbilicus with the patient in the supine position. ImageJ software was used to measure pixels with densities in the -190 Hounsfield units to -30 Hounsfield units range to delineate the visceral compartment and to compute the cross-sectional area of each in cm^2. On multivariate analysis, high visceral fat area was independently associated with shorter time to progression and overall survival. Visceral fat area measured before starting first-line targeted therapy is likely to be a simple predictive biomarker in patients with metastatic renal tumor [33].

Finally, hyponatremia seem to represent significant predictive factor for cancer-specific survival in metastatic renal tumors treated with targeted therapy as first-line therapy [34]. A total of 87 patients treated with targeted therapy including sunitinib, severe (≤ 134 mEq/L) and mild (135-137 mEq/L) hyponatremia was shown to be significantly associated with cancer-specific survival time ($P = 0.001$ and 0.013, respectively). In 38 patients treated wth sunitinib, 4 patients (10.5%) developed severe hyponatremia and 8 patients (21.1%) developed mild hyponatremia. Hyponatremia could be easily and readily determined and might be an important prognostic factor [34].

4. Conclusions

Candidate biomarkers to predict response to sunitinib have been shown. Among clinical factors, CRP is a significant independent prognostic indicator for sunitinib. Severe adverse events, hypertension and hypothyroidism also recognized as biomarkers of favorable efficacy. Additionally, tumor enhancement, SUV_{max} on FDG/PET-CT, tumor size, visceral fat area and hyponatremia have been revealed clinical significance of sunitinib responses. Although further investigation will be required, these biomarkers can be utilized to measure therapeutic response and design treatment strategies for advanced renal tumors treated with sunitinib.

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