Chronic Renal Failure / Nephrotoxicity Under Anti-VEGF-TKI Directed Treatment

Christian Kollmannsberger MD FRCPC

Clinical Associate Professor of Medicine
Div. of Medical Oncology
BC Cancer Agency-Vancouver Cancer Centre
Dept. of Medicine, University of British Columbia

Associate Member
Dept. of Urologic Science, University of British Columbia
Vancouver, Canada

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Disclosure

Consultant:

Pfizer, Novartis, Glaxo-SmithKline,

Objectives

1. To review the incidence and types of renal toxicity with various TKIs

2. Discuss the patho-mechanism of nephrotoxicity of TKIs

3. Review management options for TKI nephrotoxicity

Background

Approximately 50% of patients have an impaired kidney function prior to start with anti-angiogenic agents

Does not appear to impact efficacy !

Pre-existing impaired kidney function as risk factor ?

McFarlane, Heng, Kollmannsberger et al Cancer 2012

Sunitinib: Dosing in Renal Failure

- Phase 1 study including subjects with normal kidney function, significantly impaired kidney function (GFR <30) and patients on hemodialysis
  - Sunitinib PK in patients with severe renal impairment/hemodialysis similar to patients with normal renal function
  - Plasma exposure to sunitinib appeared lower in patients with renal failure and hemodialysis than in normal patients
  - Sunitinib not eliminated by hemodialysis
  - In hemodialysis, patients dosing based on individual tolerability

1. Bello C, et al. AACR Meeting Abstracts. 2007;LB-354 (Abstract).
2. Khosravan R, et al. J Clin Oncol. 2008;36(Suppl 15s):2578 (Abstract).
3. Gupta S, et al. J Clin Oncol. 2009;27(Suppl 15s):5108 (Abstract).
4. Josephs HD, et al. J Clin Oncol. 2009;27(Suppl 15s):5109 (Abstract).

Renal Toxicity – Clinical Symptoms

- **Renal dysfunction, including proteinuria, hyponatremia, hypophosphatemia, elevated creatinine observed with all TKIs[1-7]**
  - **Proteinuria reported in 7-11% of patients,**
  - **Elevated creatinine reported in 55-70% of patients,**
  - **Electrolyte imbalances varies**

1. Motzer RJ et al. *J Clin Oncol*. 2009;27:3584-3590. **2.** Escudier B et al. *J Clin Oncol*. 2009;27:3312-3318. **3.** Sternberg CN. *J Clin Oncol*. 2010;28:1061-1068. **4.** Rini BI et al. *Lancet*. 2011;378:1931-1939. **5.** Hudes GR et al. *J Natl Comp Cancer Netw*. 2011;9:S1-29. **6.** Kelly RJ et al. *Target Oncol*. 2009;4:121-133. **7.** Inlyta® Prescribing Information. New York, NY: Pfizer, Inc; Jan 2012.

Renal Toxicity: Common Toxicity Criteria

Adverse Event	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					

CTCAE 4.03 - June 14, 2010 : http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Incidence of Nephrotoxicity of TKI's in Pivotal Studies

TKI	Elevated creatinine All grade	Elevated creatinine ≥ grade 3
Sunitinib[1,3]	46%-66%	≤ 1%
Sorafenib[2]	41%	≤ 1%
Pazopanib[3]	32%	≤ 1%
Axitinib[2]	30-55%	0
Tivozanib[4]	70%	≤ 1%

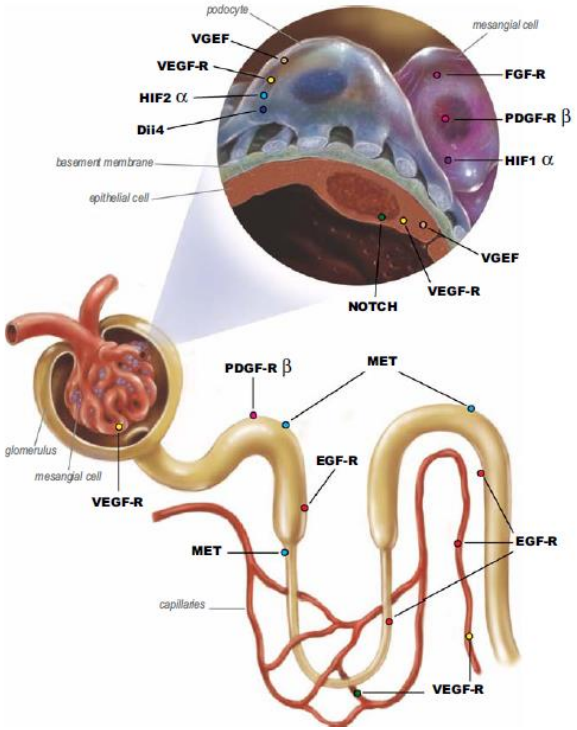
[1]Motzer et al NEJM 2007; [2]Rini et al Lancet 2011; [3]Motzer et al ESMO 2012; [4]Nosov et al JCO 2012

Renal Toxicity: Pathology

- Thrombotic microangiopathy
- Acute interstitial nephritis
- Acute Tubular Necrosis / Acute Renal Failure
- Glomerulonephritis (Mesangio-proliferative/immune complex….)
- Focal Segmental Glomerulosclerosis

Chen et al Case Rep Oncol 2009; Choi et al Cancer Res Treat 2008; Kawsar et al Med Oncol 2012; Costero et al Nephrol Dial Transplant 2010

Renal Toxicity: Pathomechanism



- VEGFR, PDGFR, c-MET and others are commonly expressed on the nephron
- VEGF is highly expressed in the glomerula
- Co-expression of these membrane targets or shared intracellular pathways between normal tissue and RCC cells may explain the occurrence of nephrotoxicity

Kelly RJ et al. *Target Oncol*. 2009;4:121-133.

VEGF function in the Kidney

- VEGF plays an important role in maintaining renal function
- Inhibition of VEGF leads to an alteration of the microvasculature and in blood vessel regression
- VEGF plays an integral role in the normal functioning of fenestrated endothelial cells
  - Altered podocytes morphology
  - Swollen endothelial cells
  - Alteration of fenestrated endothelium

Machado et al PLOS ONE 2012
Kelly et al Targ Oncol 2009;

Thrombotic Microangiopathy

VEGF signaling is a critical pathway for normal kidney function

VEGF induces the formation of fenestrations in glomerular endothelial cells

Fenestrations are necessary for the unique permeability characteristics of the glomerular filtration barrier

Loss of VEGF from the glomerulus leads to a loss of the healthy fenestrated phenotype and promotes the development of microvascular injury and thrombotic microangiopathy

Eremina et al NEJM 2009

Thrombotic Microangiopathy

- Proteinuria (low grade to nephrotic range)
- Hypertension
- Slowly rising serum creatinine (mild to moderate renal failure)
- May not be associated with hematologic features of TMA (hemolytic anemia, thrombocytopenia, schictiocytes)
- Described with sunitinib, sorafenib, cediranib…..

Appears reversible after cessation of TKI therapy !

Chen et al Case Rep Oncol 2009; Choi et al Cancer Res Treat 2008; Kawsar et al Med Oncol 2012

Preclampsia-like Syndrome

- Hypertension, Proteinuria, peripheral edema, hypoalbuminemia
- In animals the glomerular lesion associated with anti-VEGF therapy is very similar to the “glomerular endotheliosis” seen in preeclampsia
- Appeared after a median of 24-27 weeks into the treatment
- No serologic evidence of glomerulonephritis or microangiopathic hemolytic anemia
- Reversible with dose reduction or drug discontinuation

Patel et al JNCI 2008; Castilla et al Life Sci 2000

Renal Toxicity: Initial Assessment

- Evaluate risk of nephrotoxicity
    - Include history of co-morbidities e.g. hypertension, diabetes, nephrectomy, prior nephrotoxic chemotherapy
- Assess pre-exisiting kidney problems
- Elevated blood pressure should be controlled
- Perform urinalysis and creatinine / GFR at baseline
- Rule out uretheric obstruction

Renal Toxicity: Assessment on Treatment

- Assess
  - Monitor serum creatinine
  - Monitor for development of proteinuria
  - Monitor for development / progression of hypertension
  - Monitor urine analysis

On a regular basis e.g. every 4-8 weeks

Management

- Avoid potentially nephrotoxic drugs
- Manage hypertension
- For mild to moderate nephrotoxicity (CTC grade 1 and 2) continue treatment, symptomatic management , consider schedule change for grade 2 toxicity (e.g. 14/7 days)
- Grade 3, interrupt treatment until recovered , then lower dose
- In rare cases of nephrotic syndrome, acute renal failure, or organ damage, as well as other grade 4 toxicity consider drug discontinuation
- Appears partly / fully reversible in most cases

Eremina et al NEJM 2008; Izzedine et al Eur J Cancer 2010; Rixe Targ Oncol 2009; Kawsar et al Med Oncol 2012

TKI Induced Renal Failure – Reduced Efficacy ?

	CR	PR	SD	Median PFS (months)
RI at start of treatment, *n* (%)	0	5 (24)	13 (62)	10.2
RI developed during treatment, *n* (%)	1 (6)	5 (28)	10 (56)	10.2

No decrease in efficacy observed

Khan et al Ann Oncol 2010

TKI Induced Renal Failure – Increased Toxicity?

Patients with elevated creatinine at start of treatment

Patients with elevated creatinine during treatment

Toxicity	RI at start of treatment				RI developed during treatment			
	Sorafenib ($n = 13$)		Sunitinib ($n = 8$)		Sorafenib ($n = 2$)		Sunitinib ($n = 16$)	
	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)
Fatigue	10 (77)	0	7 (88)	2 (25)	1 (50)	0	14 (88)	1 (6)
HFS	8 (62)	2 (15)	3 (38)	1 (13)	1 (50)	0	8 (50)	0
Diarrhea	6 (46)	0	4 (50)	0	1 (50)	0	9 (56)	0
Nausea	4 (31)	0	4 (50)	0	1 (50)	0	6 (38)	0
HTN	4 (31)	1 (8)	2 (25)	0	1 (50)	0	8 (50)	3 (19)
Mucositis	2 (15)	1 (8)	2 (25)	0	0	0	7 (44)	0

No increase in toxicity observed in either patient group

Khan et al Ann Oncol 2010

Open Questions:

- Risk factors for Nephrotoxicity ?
  - ✓ Pre-existing kidney damage ?
- Increased incidence on sequential therapy ?
  - ✓ No excess nephrotoxicity, neither mTOR nor TKI reported on second line trials
- Cumulative worsening over time ?
  - ✓ Very few long-term grade 3 / 4 toxicities reported and no excess treatment discontinuation due to renal failure
- Management ?
  - ✓ ACE-inhibitors ? Other nephroprotection ?

Conclusions

- Significant renal toxicities secondary to targeted molecular therapies exist
- TKIs can be safely administered , provided ongoing monitoring for renal function
- Creatinine elevations may require dose or schedule adjustments
- Severe nephrotoxicity is rare
- Nephrotoxicity appears partly / fully reversible upon termination of therapy
- Clinical outcome (efficacy and toxicity) appears uncompromised