Primary Care Management of the Kidney Cancer Patient

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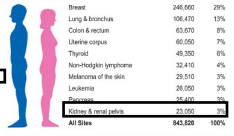
Learning Objectives

1. Understand the mechanisms of action of currently approved drugs for metastatic renal cell carcinoma (mRCC).
2. Be able to assess and manage side effects of:
   a. Vascular endothelial growth factor (VEGF)-signaling inhibitors
   b. Mammalian target of rapamycin (mTOR) inhibitors
   c. Programmed cell death protein 1 (PD-1) inhibitors

Kidney Cancer in 2016

- Estimated New Cases in US: 62,700
- Estimated Deaths in US: 14,240

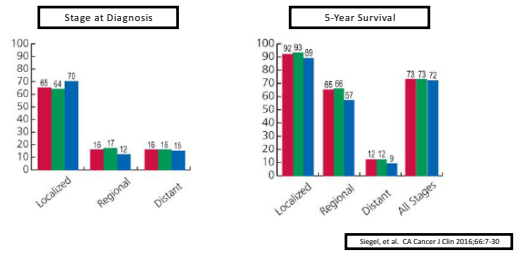
Estimated New Cases



Males			Females		
Prostate	180,890	21%	Breast	246,660	29%
Lung & bronchus	117,920	14%	Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%	Colon & rectum	63,670	8%
Urinary bladder	58,950	7%	Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%	Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%	Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,590	5%	Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,700	4%	Leukemia	26,050	3%
Leukemia	34,090	4%	Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%	Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**	**All Sites**	**843,820**	**100%**

Siegel, et al. CA Cancer J Clin 2016;66:7-30

Early Diagnosis Improves Survival



Siegel, et al. CA Cancer J Clin 2016;66:7-30

Approved Therapies for mRCC

- 1992: High-Dose Interleukin-2 (HD IL-2)
- 2005: Sorafenib
- 2006: Sunitinib
- 2007: Temsirolimus
- 2009: Everolimus
- 2009: Bevacizumab + Interferon (IFN)
- 2009: Pazopanib
- 2012: Axitinib
- 2015: Nivolumab
- 2016: Cabozantinib
- 2016: Lenvatinib + Everolimus

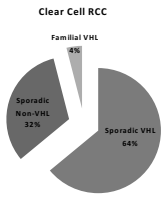
mRCC Therapies by Mechanism of Action

Anti-angiogenesis (VEGF-signaling) Inhibitors:
- Sorafenib
- Sunitinib
- Bevacizumab
- Pazopanib
- Axitinib
- Cabozantinib
- Lenvatinib

mTOR Inhibitors:
- Everolimus
- Temsirolimus

Immunotherapy:
- High-dose IL-2
- Nivolumab

VHL Mutation Mediates Development of RCC



Mutated VHL protein

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Accumulation of hypoxia-inducible factor (HIF) protein

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HIF-mediated transcriptional activation of VEGF, PDGF, TGF-β, other genes

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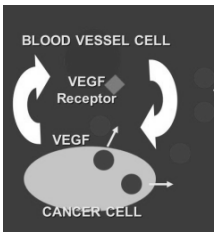
Angiogenesis, autocrine growth, and survival of cancer cells

VEGF/R Inhibitors Block Tumor Angiogenesis



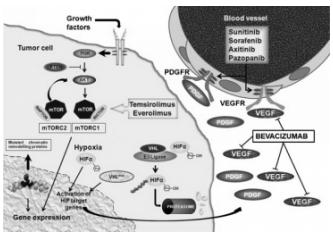
Anti-VEGF antibody:

- Bevacizumab

Anti-VEGFR small molecule TKIs:

- Sorafenib
- Sunitinib
- Pazopanib
- Axitinib
- Cabozantinib
- Lenvatinib

mTOR Inhibitors Block HIF Production and Slows Tumor Growth

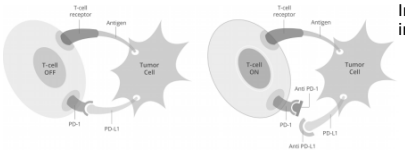


mTOR inhibitors:

- Everolimus
- Temsirolimus

MedoGene.com, accessed 10/2016

PD-1 Inhibitors Allow Re-activation of the Immune T cells



Immune checkpoint inhibitors:

- Nivolumab (PD-1)
- Ipilimumab* (CTLA-4)
- Atezolizumab* (PD-L1)
- Pembrolizumab* (PD-1)

*In development, but not approved yet for mRCC.

SmartPatients.com, accessed 10/2016

Important Side Effects of VEGF/VEGFR Inhibitors

- Constitutional:
  - Fatigue
  - Hair changes
  - Anorexia and dysgeusia
  - Hoarseness
- GI/Hepatic:
  - Diarrhea
  - Nausea and/or vomiting
  - Reflux
  - GI Perforation
  - AST/ALT Elevation
  - Increased lipase/amylase
- Cardiovascular:
  - Hypertension
  - Fluid retention (e.g. periorbital edema)
  - Congestive heart failure
  - QTc prolongation
  - Cardiac ischemia/infarct
  - Arrhythmia
  - Arterial or venous thromboembolic event
  - Posterior reversible leukoencephalopathy syndrome

Important Side Effects of VEGF/VEGFR Inhibitors

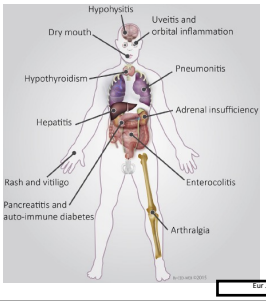
- Mucocutaneous:
  - Mucositis
  - Hand-foot skin reaction
  - Skin discoloration
  - Impaired wound healing
- Renal:
  - Proteinuria
  - Acute kidney injury
- Hematologic:
  - Anemia, leukopenia, thrombocytopenia
  - Bleeding or thrombosis
- Endocrine:
  - Hypothyroidism or hyperthyroidism
  - Hypoglycemia

Important Side Effects of mTOR Inhibitors

- Fatigue
- Stomatitis
- Skin rash
- Diarrhea, Nausea, Vomiting, Anorexia
- Hyperlipidemia/hypertriglyceridemia
- Hyperglycemia
- Cough, Dyspnea, Interstitial pneumonitis
- Increased creatinine
- Increased risk of infection

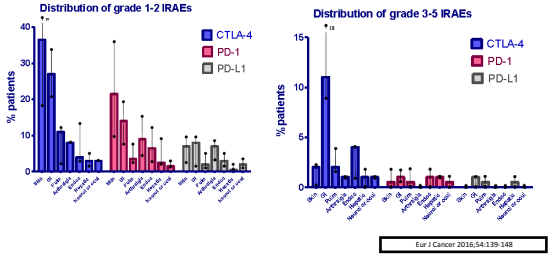
Important Side Effects of Immune Checkpoint Inhibitors

- Fatigue
- Skin and mucosal
- Gastro-intestinal
- Endocrine
- Liver
- Lung
- Renal
- Pancreatic
- Eye and Neurologic
- Polyarthritis
- Hematologic



Eur J Cancer 2016;54:139-148

Immune Mediated Adverse Events: Inter-agent differences in incidence and severity



Eur J Cancer 2016;54:139-148

Side Effect Management

- Consider the severity
- Consider the mechanism of action of the drug
- Consider alternative causes
- Supportive measures and medical management
- Dose interruption and/or reduction often required

Case Study 1: Hypertension

A 60 y/o woman with metastatic renal cell carcinoma and history of left nephrectomy is started on pazopanib. Her creatinine is 1.5 and her urinalysis shows 2+ protein. She develops new onset hypertension with BP measurements of 170/100 and 168/94 on her last two visits.

What would be the optimal initial choice of anti-hypertensive?

1. Hydrochlorothiazide
2. Furosemide
3. Metoprolol
4. Lisinopril

Case Study 1: Hypertension

She starts lisinopril 20mg/day and required up-titration to the 40mg/day. She continues to have elevated blood pressures 156/92, 160/96.

What would be the next choice of anti-hypertensive?

1. Stop lisinopril and switch to losartan
2. Stop Lisinopril and switch to nifedipine
3. Continue lisinopril and add amlodipine
4. Continue lisinopril and add amlodipine

VEGF/VEGFR Inhibitor-Induced Hypertension

- Characteristics
  - Occurs rapidly within hours to days and may be severe
  - SBP affected more than DBP
  - May be resistant to anti-hypertensive therapy
  - Withdrawal of VEGF/R-inhibitor leads to rapid decrease in BP
  - Degree of hypertension may be predictive marker of response
- Risk Factors
  - Previous history of hypertension
  - Combination therapy with >1 anti-VEGF/R agent
  - Age > 65 years
  - Smoking
- Mechanisms
  - Suppression of VEGF mediated vasodilatory pathways
  - Suppression of nitric oxide production

VEGF/VEGFR Inhibitor-Induced Hypertension

- Management
  - Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers
  - Vasodilators
    - Dihydropyridine calcium channel blockers preferred (amlodipine or nifedipine)
    - Verapamil may not be effective
    - Avoid nitrates (may compromise anti-angiogenic effect of anti-VEGF therapy)
  - Thiazide diuretics
    - Avoid furosemide (efficacy may be impaired by NO inhibition of anti-VEGF therapy)
- Consider compelling indications

VEGF/VEGFR Inhibitor-Induced Hypertension

1. Continue current medication/s
2. If 2 BP readings > 150/100 mm Hg or diastolic BP has increased > 20 mm Hg from baseline
   a. Increase current medication until maximum dose **
   b. If BP is still not < 150/100 mm Hg or diastolic BP has increased > 20 mm Hg from baseline than follow below

If Currently Taking:	Add or Switch to:
Thiazide or Diuretic, (avoid furosemide)	ACE-I or ARB
ACE-I or ARB	dCCB (eg, Nifedipine, Amlodipine)
β-Blocker and/or CCB	ACE-I or ARB and/or dCCB
Thiazide + ACE-I or ARB	dCCB (eg, Nifedipine, Amplodipine)
Thiazide + β-Blocker	ACE-I or ARB and/or dCCB
ACE-I or ARB + CCB	dCCB and or BB (prefer nebivolol)
β-Blocker + ACE-I or ARB	dCCB (eg, nifedipine, amlodipine)
Thiazide + ACE-I or ARB + CCB	BB (prefer nebivolol) or dCCB
Thiazide + ACE-I or ARB + CCB + BB	Direct vasodilator (eg, hydralazine)
α-1-selective blocker	ACE-I or ARB and/or dCCB

Clinical Colorectal Cancer 2011;10:151-6

VEGF/VEGFR Inhibitor-Induced Hypertension

Not on any Medication for Hypertension:

If 2 BP readings > 150/100 mm Hg or diastolic BP increased by > 20 mm Hg from baseline:

a. Start first-line therapy as indicated in the second column below and increase medication until maximum dose.**

b. If BP still not < 150/100 mm Hg or diastolic BP has increased > 20 mm Hg from baseline, then follow the third column below.

Comorbid Condition:	First-line:	Add or Switch to:
None	Thiazide (avoid furosemide)	ACE-I or ARB and/or dCCB
History of myocardial infarction	ACE-I or ARB	BB (nebivolol) and/or dCCB
Heart failure	Thiazide + ACE-I or ARB	BB (prefer nebivolol)
Chronic kidney disease	ACE-I or ARB	BB and/or dCCB
Diabetes	Thiazide (avoid furosemide)	ACE-I or ARB
Left ventricular dysfunction	ACE-I or ARB	BB and/or dCCB
History of stroke	ACE-I or ARB	BB and /or dCCB and/or direct vasodilator (eg, hydralazine)
Osteopenia, osteoporosis, asthma, COPD	ACE-I or ARB	BB and/or dCCB and/or direct vasodilator (eg, hydralazine)

Abbreviation: COPD = chronic obstructive pulmonary disease.

Clinical Colorectal Cancer 2011;10:151-6

Case Study 2- Pneumonitis

A 72 y/o male with metastatic renal cell carcinoma has taken everolimus 10mg/day for 3 months. He presents with a moderate dry cough and dyspnea on exertion that has been progressive for 4 weeks. His O2 sat is 92% on RA. CT chest shows new patchy pulmonary infiltrates and bilateral hilar lymphadenopathy.

What do you do next?

1. Hold everolimus and consult pulmonology for diagnostic bronchoscopy.
2. Switch to temsirolimus.
3. Start high-dose steroids and continue everolimus at 10 mg/day.
4. Reduce everolimus to 5 mg/day and follow up in 2 weeks.

Management of Pneumonitis

- mTOR-related pneumonitis
  - Hold treatment
  - Pulmonary referral to rule out infectious etiology
  - Corticosteroids
- Immune-mediated pneumonitis
  - Hold treatment
  - If moderate or severe symptoms:
    - Start high dose corticosteroids
    - Prophylactic antibiotics
    - Consider bronchoscopy and lung biopsy
    - If not responding, consider non-corticosteroid immunosuppressive medication

Management of Fatigue

- Rule out anemia, dehydration, electrolyte imbalances, diarrhea, hypothyroidism, adrenal insufficiency, heart failure, malnutrition, etc.
- Non-Pharmacological
  - Exercise (yoga, aerobic exercise)
  - Massage therapy
  - Cognitive behavioral therapy and psycho-educational therapies
  - Consider referrals to PT/OT and nutrition
- Pharmacological
  - Psychostimulants
  - Optimize treatment for sleep dysfunction, malnutrition, comorbidities

NCCN Guidelines Cancer-Related Fatigue v 1.2016

Management of Diarrhea

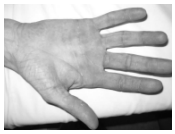
- VEGF- and mTOR-related diarrhea
  - Dietary measures
  - Avoidance of certain foods or drinks
  - Loperamide +/- Diphenoxylate/atropine
  - Dose interruption and/or reduction
- Immune-mediated diarrhea/colitis
  - Mild- supportive measures, loperamide
  - Moderate- supportive measures, loperamide, steroids
  - Severe/Life-threatening- inpatient admission, IV hydration, IV steroids +/- Infliximab (anti-TNF-α), consult gastroenterologist and surgery

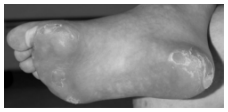
Management of Stomatitis

- Ensure good oral hygiene
- Avoid mouthwashes containing alcohol
- Avoid hot, spicy, or acidic foods
- When appropriate, use of mouthwashes containing:
  - Steroids
  - Anesthetics
  - Antibiotics
  - Antifungals

Hand-Foot Skin Reaction

- Grade 1
  - Mild redness, swelling, or tingling
- Grade 2
  - Painful, skin intact
  - Limiting instrumental ADLs
- Grade 3
  - Severe pain, tissue breakdown
  - Limiting self-care ADLs





Support Care Cancer (2015) 23:1829

Management of Hand-Foot Skin Reaction

- Moisturize hands and feet
- Urea-based creams
- Avoid rubbing (e.g. ill-fitting shoes)
- Avoid hot showers
- Analgesic use (topical or systemic)
- Wound care if appropriate
- Antibiotics if appropriate
- Consider referrals to dermatology and/or podiatry

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