# SYSTEMIC THERAPY OPTIONS FOR BLADDER AND KIDNEY CANCER PATIENTS

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## EDUCATIONAL OBJECTIVES

- Differentiate between chemotherapy, immunotherapy, and targeted therapies
- Identify factors that influence the choice of treatment for patients
- Become familiar with treatments for metastatic bladder cancer
- Become familiar with treatments for metastatic renal cancer
- Learn common adverse effects of various treatments

## A WORD ABOUT CHEMOTHERAPY

The therapeutic use of chemical agents to treat disease

Merriam-Webster (2018)

**A treatment utilizing chemicals to stop cancer cell growth by killing cells or stopping cell division**

NIH, National Cancer Institute (2018)

## CHEMOTHERAPY

Commonly chemotherapy agents in Bladder Cancer:

- Cisplatin, Carboplatin
  - Alkylating agents: attach an alkyl group the cancer cell's DNA and inhibits cell growth
  - Platinum analogues
- Gemcitabine
  - Antimetabolites: stops cells from making DNA

(NIH, National Cancer Institute, 2018)

## MORE CHEMOTHERAPY

Bladder Cancer continued…

- Doxorubicin
  - Anthracycline antitumor antibiotic: damages DNA of cancer cells
- Vinblastine
  - Vinca Alkaloid: antimitotic agent
- Methotrexate
  - Antibmetabolite and antifolate: inhibits DNA and RNA synthesis

(NIH, National Cancer Institute, 2018)

## AGAIN WITH THE CHEMOTHERAPY

2nd Line Bladder Cancer:

- Paclitaxel, Docetaxel
  - Taxanes: interfered with microtubules which are needed for mitosis thus inhibiting mitosis
- Pemetrexed
  - Folate antagonist; stops cancer cells from using folic acid to make DNA

For less common histological types of bladder cancer:

- FOLFOX, regimens containing Etoposide, or Ifosfamide

(NCCN, 2018; NIH, National Cancer Institute, 2018)

# BUT WAIT, THERE'S MORE

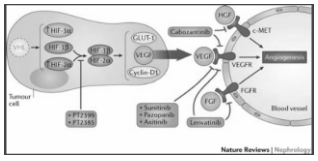
OUT THERE BESIDES CHEMO

## TARGETED THERAPY

- Targets specific genes or proteins which stop the growth of cancer
- Less harm to normal cells than chemo
- Many drugs given orally
- Commonly used in Kidney Cancers

NIH, National Cancer Institute, 2018

## TARGETED THERAPY IN KIDNEY CANCER




- Renal Cell tumors have a large network of abnormal blood vessels
- Vascular Endothelial Growth Factor is overexpressed, it binds to receptors on blood vessels, and activates intracellular tyrosine kinases triggering tumor angiogenesis

Lee & Motzer, (2017)

# TARGETED THERAPY

**VEGF OR TYROSINE KINASE INHIBITORS**

- Sunitinib
- Pazopanib
- Axitinib
- Cabozantinib

**MTOR INHIBITORS**

- Everolimus
- Temsiroliums

# IMMUNOTHERAPY

Monoclonal antibodies which target receptors and block the binding of tumor cells to T cells

T Cells are kept activated and immune response to tumor cells is increased

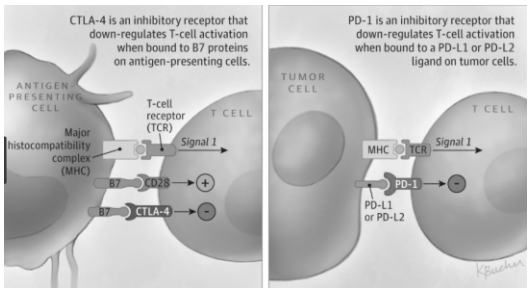



Image Retrieved from: Jacob JA. Cancer Immunotherapy Researchers Focus on Refining Checkpoint Blockade Therapies. *JAMA* 2015;314(20):2117–2119. doi:10.1001/jama.2015.10795

## IMMUNOTHERAPY

Drugs commonly used in Bladder, Kidney and many other solid tumor cancers:

- CTLA-4 INHIBITORS - Ipilimumab
- PD-1 INHIBITORS – Pembrolizumab, Nivolumab
- PD-L 1 IINHIBITORS - Atezolizumab

# BLADDER CANCER

**SYSTEMIC TREATMENT**

## FACTORS THAT INFLUENCE TREATMENT CHOICE - BLADDER

- Staging: Non muscle invasive, Muscle Invasive, Metastatic
- Pathology: Urothelial/transitional cell or mixed (most), squamous, adenocarcinoma, small cell
- Patient considerations: performance status, cardiac or renal function, comorbidities
- PD-L1 Immunohistochemistry

## BLADDER CANCER STAGING

| Non Muscle Invasive | Muscle Invasive | Metastatic |
|---|---|---|
| 70-75% of cases | 20% of cases | 4-5% of cases |
| 70% 5 year survival | 15% 5 year survival | 5% 5 year survival |
| Treatment goal: curative | Treatment goal: cure, prevent progression | Treatment goal: Palliation |

NCCN Guidelines, Bladder Cancer (2018); Kamat (2016)

## HISTOLOGY OF BLADDER CANCER

>90% is urothelial / transitional cell or mixed

5-10% is pure squamous, pure adenocarcinoma, or small cell

## METASTATIC BLADDER CANCER

**CYTOTOXIC CHEMOTHERAPY**

- 1st line if cisplatin eligible:
  - ddMVAC
  - Gem/Cis
- 1st line if cisplatin ineligible
  - Gem/Carbo

**IMMUNOTHERAPY**

- 1st line if cisplatin ineligible AND high PD-L1 expressing tumor
  - Pembrolizumab
  - Atezolizumab

NCCN Guidelines, Bladder Cancer (2018)

The FDA has issued a drug safety notification warning against the use of frontline single-agent immune checkpoint inhibition for patients with PD-L1–low expressing platinum-eligible urothelial carcinoma, following a demonstration of lower overall survival with pembrolizumab (Keytruda) and atezolizumab (Tecentriq) compared with platinum-based chemotherapy.

US Food and Drug Administration, 2018

## CISPLATIN ELIGIBILITY

- Creatinine Clearance >50ml/min
- Ejection fraction >45%
  - Also pertains to Doxorubicin which can be cardiotoxic
- Peripheral Neuropathy > Grade 3
- Hearing Loss
- Performance Status 3+

NCCN Guidelines,Bladder Cancer (2018)

- Hematologic
- Gastrointestinal
- Nervous system
- Nephrotoxicity
- Cardiotoxicity
- Fatigue

## CHEMOTHERAPY TOXICITIES

## CHEMO- HEME TOXICITY

Myelosuppression is a side effect of chemotherapy occurring 7-14 days after treatment

- Neutropenia
  - ANC <1500
- Thrombocytopenia
  - Platelets <100K
- Anemia
  - Hgb <12

Polovich, Whitford & Olsen (2014)

## CHEMO- GI TOXICITY

Nausea/Vomiting

- Drugs have varying emetogenicity
- Patient receive combination of IV anti-emetics + oral
- Anti-emetics:
  - Fosaprepitant, Ondansetron, Palonsetron, Dexamethasone, Olanzapine
  - Cannabinoids/ Cannabis
  - Progressive muscle relaxation and guided imagery
  - Patient education to manage expectations

Oncology Nursing Society (2017)

## CHEMO- GI TOXICITY

Mucositis

- Inflammation of mucus membranes of oral cavity and GI tract
- Incidence 40% of those getting chemo, dose limiting side effect
- Cryotherapy; Good oral care

Constipation

- Opioids or not?
- Polyethylene glycol, Senna, Docusate, Amidotrizoate

Diarrhea

- Loperamide
- Encourage Hydration, Monitor for dehydration
- BRAT diet

Oncology Nursing Society (2017)

## CHEMO- NERVE TOXICITY

**PERIPHERAL NEUROPATHY**

- Platinum analogs, taxanes and vinca alkaloids
- >10% will develop pain, numbness, tingling, gait/balance problems
- Duloxetine; Gabapentin, Opioids most effective treatment

**OTOTOXICITY**

- Platinum analogs and vinca alkaloids
- Hearing loss, tinnitus, vertigo
- Audiology Exam

O'Leary, 2014; Oncology Nursing Society (2017)

## CHEMO- NEPHROTOXICITY

- 20% of patients receiving higher doses of cisplatin have severe renal dysfunction
- Causes injury to the proximal tubules leading to decrease in glomerular filtration may be reversible
- Electrolyte imbalances
- Prevent with vigorous hydration
- Avoid NSAIDs and other nephrotoxic drugs

Yao et al. (2007)

## CHEMO- CARDIOTOXICITY

- Anthracyclines (such as Doxorubicin) are the greatest culprit
- Acute
  - Transient ST and T wave changes, decreased QRS voltage, prolonged QT interval, sinus tachycardia, supraventricular arrhythmias
- Delayed
  - Usually occurs within a year of treatment but can occur decades after chemo
  - Chronic dilated cardiomyopathy, ventricular dysfunction, heart failure, arrhythmias

Carvalho et al. (2014)

## CHEMO- CARDIOTOXICITY

Management:

- Educate patient on risks and signs of cardiac dysfunction
- Recognize Early
- Dexrazoxane
- Cumulative life time dose of doxorubicin is <550mg/m2

Polovich, Whitford & Olsen (2014)

## AND MANY MORE… CHEMO TOXICITIES

- Fatigue
- Alopecia
- Rashes and other skin changes
- Infusion reactions
- Sexual Dysfunction/ Fertility Issues
- Possible drug interactions

## IMMUNOTHERAPY TOXICITIES

# IMMUNOTHERAPY TOXICITIES

| | | | | |
|---|---|---|---|---|
| Dermatitis | Colitis | Hepatitis | Endocrinopathies | Pneumonitis |
| Nephritis | Uveitis, Episcleritis, Blepharitis | Nervous system: | Cardiovascular | Musculoskeletal: |

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - DERMATOLOGIC

| Assessment | Management |
|---|---|
| Mild<br>- <10% of BSA with/without symptoms | Continue immunotherapy<br>Topical Steroids<br>Oral Antihistamine<br>Emollient |
| Moderate<br>- 10-30% BSA with or without symptoms | Consider holding treatment<br>High potenty topical steroids or prednisone<br>Oral antihistamine<br>Emollient |
| Severe<br>- >30% BSA, limiting self-care ADLs | Hold Immunotherapy<br>High potency topic steroid + prednisone<br>Derm referral |

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - COLITIS

| Assessment | Management |
|---|---|
| Mild<br>Asymptomatic, <4 stools/day | Bland diet; Loperamide<br>Instruct patient to monitor for worsening |
| Moderate<br>Abdominal Pain<br>Mucus/Blood in Stool; 4-6 stods/day | Hold Immunotherapy<br>Stool cultures, routine bloodwork<br>Oral Prednisone or Budesonide |
| Severe | Hold Immunotherapy; cultures and bloodwork<br>IV methylprednisolone 1-2mg/kg/day<br>Convert to PO taper over 4-6wks |
| Life-threatening | Permanently discontinue Immunotherapy<br>IV steroids 2-4mg/kg/day<br>Infliximab 5mg/kg |

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - HEPATITIS

| Assessment | Management |
|---|---|
| Mild<br>AST, ALT elevated but <3 ULN; T Bili <1.5 ULN | Monitor LFTs weekly |
| Moderate<br>AST, ALT 3-5x ULN, T Bili 1.5-3x ULN | Hold Immunotherapy<br>Monitor LFTs twice weekly<br>Rule out viral hepatitis or disease progression<br>Oral Prednisone 0.5-1 mg/kg/day x 4 wks min |
| Severe<br>AST, ALT >5x ULN<br>T Bili >3x ULN | Permanently Discontinue Immunotherapy<br>Monitor LFTs every 1-2 days<br>Prednisone 1-3 mg/kg/day either IV or PO<br>Hepatology Consult<br>If no improvement after 3 days of steroids, mycophenolate |

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - ENDOCRINOPATHIES

- Thyroid
  - Monitor hyperthyroid unless symptomatic; often converts to Hypothyroid
  - Hypothyroid: levothyroxine if TSH > 10, monitor TSH with reflex T4 every 4-6 weeks
- Type 1 Diabetes
  - Hold therapy, treat with insulin, may resume if fasting BG was <250 and no DKA
  - Consult Endocrine
- Hypophysitis
  - Inflammation of pituitary
  - Consult Endocrine

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - PNEUMONITIS

| Assessment | Management |
|---|---|
| Mild<br>Asymptomatic<br>Incidental finding on CT | Hold Immunotherapy and reassess in 1-2 wks<br>Repeat imaging each cycle<br>Monitor pulse ox weekly |
| Moderate<br>Symptomatic, Limiting IADLs | Hold Immunotherapy<br>Pulmonary referral, Infectious workup<br>Prednisone 1 mg/kg/day taper over >4 weeks |
| Severe or life-threatening | Permanently Discontinue<br>Pulmonary referral<br>IV or PO steroids 1-2 mg/kg/day |

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES - CARDIOVASCULAR

**Immune Checkpoint Inhibitors: Game Changing Cancer Therapy With a Cardiac Cost. What Are the Mechanisms and Unresolved Questions in Cardiotoxicity?**

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- Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function
- ALL REQUIRE HOSPITAL ADMISSION
- Check Troponins at baseline
- Referral to cardiology

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# MANAGEMENT OF IMMUNOTHERAPY TOXICITIES – NERVOUS/MSK

**NERVOUS**

- Myasthenia gravis
- Guillain-Barre
- Peripheral neuropathy
- Aseptic meningitis
- Encephalitis
- Transverse myelitis

**MUSCULOSKELETAL**

- Inflammatory arthritis
- Myalgias

NCCN Guidelines version 1.2018 Management of Immunotherapy-Related Toxicities

# KIDNEY CANCER

**SYSTEMIC TREATMENT**

## KIDNEY CANCER

- 90% are Renal Cell Carcinoma
- 80% are clear cell histology
- 15-25% of patients have metastatic disease at diagnosis
- Classified as favorable, intermediate or poor risk based on number of prognostic factors

Siefel, 2018; Kidney Cancer Association, 2018

## KIDNEY CANCER

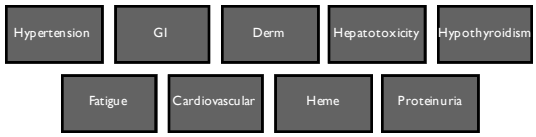
Stage IV or surgically Unresectable

1st line (Clear Cell)

- Clinical Trial
- Pazopanib 800mg daily
- Sunitinib 50mg, 4 weeks on, 2 weeks off
- Ipiliumumab + Nivolumab (intermediate or poor risk)
- Bevacizumab + interferon alfa 2b
- Temsirolimus (poor risk)
- Axitinib – 5mg BID
- Cabozantinib (intermediate or poor risk) 60mg daily
- High dose IL2

NCCN Guidelines Version 4.2018 Kidney Cancer

## VEGF INHIBITORS - ADVERSE EFFECTS



## VEGF-I & HYPERTENSION

- VEGF stimulates production of nitric oxide causing arterial vasodilation
- Highest risk for those with previous HTN- Need BP <140/<90 to start
- Monitor BP at least weekly during initial treatment period
- No non-dihydropirimidine CCBs - can have CYP interactions
- Reassess anti-hypertensives during treatment breaks

Castellano, D. et al. (2013); Larochelle et al. (2012)

## VEGF-I & GI TOXICITY

**DIARRHEA**

- 56-81% all grades sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib + everolimus
- Management:
  - Loperamide, Diphenoxylate/Atropine
  - Fiber - psyllium
  - Monitor for dehydration

**NAUSEA**

- 26-58% all grades
- Management
  - Ondansetron, prochlorperazine, olanzapine
  - Use anti-emetics as pre-medication or PRN
  - Dose VEGF-I close to bedtime

## VEGF-I & GI TOXICITY

**MUCOSITIS**

- Avoid Alcohol
- Bland diet
- Stomatitis Cocktail
- Treatment breaks if ulcers develop

**ANOREXIA**

- Small, frequent meals
- Supplementation – nutritional drinks, shakes
- Can try appetite stimulant

# VEGF-I & DERM TOXICITY

- Hand Foot Skin Reaction (palmar-plantar erythrodysesthesia syndrome)

| Grade 1 | Grade 2 | Grade 3 |
|---|---|---|
| Minimal erythema, edema, hyperkeratosis without pain | Peeling, blisters, bleeding, edema or hyperkeratosis with pain; Limits ADLs | Severe peeling, blisters, bleeding, edema, hyperkeratosis with pain; limits self care |

- Highest Incidence with Cabozantinib & Sunitinib

Castellano et al. (2013)

# VEGF-I & MANAGEMENT OF DERM TOXICITY

- Remove hyperkeratotic areas
  - pedicures and podiatry
- Protect hands and feet
  - Comfortable shoes and socks that fit
  - Gel inserts
  - Avoid friction
- Moisturize
- Avoid hot water

# VEGF-I & LIVER AND THYROID TOXICITY

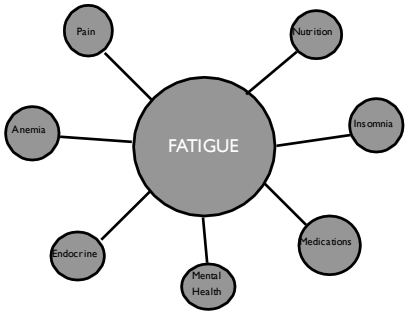
**HEPATOTOXICITY**

- Monitor Baseline LFTs and regularly during treatment (varies by drug)
- Monitor weekly if elevations occur; may require hold or dose reduction

**HYPOTHYROIDISM**

- Monitor TSH at baseline and every 3 months after
- Thyroid hormone replacement with TSH > 10mU/L or symptomatic

Hudes et al. (2011)




## MANAGEMENT OF FATIGUE

- High incidence, multifactorial
- Management:
  - Exercise
  - Educate patients
  - Energy conservation & activity management
  - Massage
  - Yoga
  - Ginseng

Arial & Escalante (2015); Oncology Nursing Society (2017)

## IPILIMUMAB + NIVOLUMAB ADVERSE EFFECTS

- Previously reviewed Immunotherapy adverse effects
- Incidence of adverse effects increases with use of multiple agents
  - Nivolumab alone: 19% have grade 3 or 4 adverse events
  - Nivo + Ipi: 46% had grade 3 or 4 adverse events

Motzer et al. (2015); Motzer at al. (2018)

## MTOR INHIBITOR ADVERSE EFFECTS

- Fatigue
- Mucositis
- Dermatologic Toxicity: Rash
- Metabolic Abnormalities: Hyperglycemia, Hypercholesterolemia, Hypertriglyceridemia
- Non-infectious pneumonitis
- Mild immunosuppression

Albiges et al. (2012)

## CONCLUSIONS

- There are MANY different options available for patients with metastatic bladder or kidney cancer.
- Treatment recommendations are always evolving, refer to NCCN guidelines and recent clinical trial data for the latest development.
- Adverse effects vary greatly based on the type of treatment.
- Familiarity with the general side effects of treatment can help us recognize and treat them as quickly as possible

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