Managing Side Effects of Cancer Therapy

Diagnosis, Management and Clinical Pearls

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Disclosures

- Medical Advisory Board Eisai
- Speaker’s Bureau: Eisai
Objectives

To understand how cancer therapy kills cancer based on cell growth physiology, cell function and immune system physiology

Define Cancer Therapy: Chemo, immunotherapy, targeted therapy, radiation therapy, surgery, monoclonal antibodies, vaccines, IMIDs, cytokines, Allogeneic HSCT, CAR-T

To manage sequelae of therapy by employing medication adjustments and/or add new medications

Discuss coordination of care with primary medical team, PMD, and consultants

Will focus on chemotherapy, immunotherapy and targeted therapy during this talk
Cell Cycle

• The Cell Cycle is an ordered set of events by which cells grow and divide into two daughter cells.

• In solid tumors cancer occurs when cellular DNA is damaged, and that damage gets replicated during the cell cycle creating a neoplasm.

• Tumor cells will continue to divide if our suppressor genes don’t pick up the error in production.
Cell Cycle

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Cell Cycle

Mitosis

- prophase
- prometaphase
- metaphase
- anaphase
- telophase & cytokinesis

- centrosome
- kinetochore
- mitotic spindle
- midbody ring

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Cancer Immunoediting
Basic Principles of Chemotherapy

- Chemo is most active on cells that divide quickly. i.e. Burkitt’s vs TB

- Fun fact: In old movies Tuberculosis was referred to as “The Consumption”

- Different chemo agents/ classes of agents work at different points during a cell cycle

- Combination chemotherapy works by interrupting the cell cycle at different points. i.e. carboplatin/ paclitaxel, doxorubicin/ carboplatin, CHOP, etc.
How Conventional Chemo Affects the Cell Cycle

Mitotic inhibitors: vinca alkaloids, taxanes

Antimetabolites: pyrimidine antagonists, antifolates, hydroxyurea, purine antagonists, purine analogues

Topoisomerase inhibitors: topoisomerase I inhibitors, topoisomerase II inhibitors

Antibiotics: actinomycin D, bleomycin

Other: L-asparaginase, bortezomib

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Understanding Checkpoints

• Checkpoints are transmembrane proteins present on T-cell, B-cells, NK cells, and multiple tissue types (normal cells, tumors, hematopoietic cells)

• PD-1 (programmed cell death protein) is on our immune cells (T, B and NK cells)

• PDL-1 (programmed death ligand) is on tissues and tumor cells. PDL-2 is on hematopoietic cells

• CTLA-4 (cytotoxic T-lymphocyte associated protein) is present on the surface of CD4+ and CD8+ T lymphocytes. CTLA-4 A.K.A CD152

• Neoplastic cells can be invisible to the immune system
Explaining Immune System Failure to “see” Tumor Cells
Commonly Used Checkpoint Inhibitors

- **PD-1**: pembrolizumab, nivolumab, and cemiplimab
- **PDL-1**: atezolizumab, avelumab, durvalumab
- **CTLA-4**: ipilimumab (monoclonal antibody)
CTLA-4 Binding and Inhibition
Chemo plus check point inhibitor

• Combination therapy to kill cancer different ways

• Chemo kills by disrupting the cell cycle and immunotherapy induces the immune system to attack

• For example, Lung cancer regimen: etoposide plus carboplatin/ cisplatin and durvalumab.
Targeted Therapy: Kinase Inhibition

- Kinases are enzymes that deliver a phosphate to a protein.
- Approximately 538 known kinases encoded in human genome. AKA “Kinome”
- Most protein kinases promote cellular proliferation and migration.
- Overexpression is associated with oncogenesis.

Cell Cycle

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VEGF

- VEGF – Vascular Endothelial Growth Factor is a kinase primarily responsible for neovascularization/angioneogenesis.

- VEGF stimulates vascular endothelium to secrete nitric oxide (NO). NO is responsible for naturesis and vasodilation.

- Common VEGF inhibitors: bevacizumab (monoclonal antibody), sorafenib, sunitinib, lenvatinib.

- VEGF involved in normal physiologic functions. Side effects occur when targeting oncogenic processes and the normal VEGF function is blocked.
Chemo plus targeted therapy

• Combination therapy to kill cancer different ways

• Chemo kills by disrupting the cell cycle and targeted therapy disrupts normal cell function by blocking the physiologic function of a target

• For Example: Breast: Taxane plus trastuzumab (HER-2 targeted agent)

• For example: Gastric: FOLFOX/FOLFIRI plus trastuzumab or bevacizumab (VEGF targeted agent)
Immunotherapy Plus Targeted Therapy

• Combination therapy to kill cancer different ways

• Immunotherapy recruits the immune system and targeted therapy disrupts normal cell physiology by blocking a target in the physiologic pathway

• For Example: Endometrial Cancer: pembrolizumab plus lenvatinib

• For Example: Renal Cell: cabozantinib and nivolumab
Tumor Agnostic

- A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body.

- Conventional therapies usually target a particular molecule in the tumor cells, in which most tumor responses last until the cancer develops a way to bypass the blocked pathway, whereas PD-1 blockade releasing negative regulators of immune checkpoints is applicable to a wide range of malignancies as well as provides long-lasting responses.

Chemotherapy side effects

- Nausea, vomiting, diarrhea (colitis), skin changes, secondary skin cancers (hematologic malignancies), weight loss, anorexia, dehydration, cytopenias, pneumonitis (i.e. methotrexate, bleomycin), hypotension/ hypertension, adrenal insufficiency, anemia

- Organ function decline: liver, kidneys, heart, bone marrow function, muscle

- Exacerbation of co-morbid conditions

- Decreased functional reserve, decreased performance status, “chemo brain”

- Infusion reactions
Clinical Pearl

• Never accept these three words:

  • Tired

  • Dizzy

  • Nauseous

• Explain the sensation of feeling tired/ dizzy/ nauseous without using the word in your explanation.
Chemotherapy related MDS/ AML

• The incidence of t-MDS/AML following conventional therapy ranges from 0.8% to 6.3% at 20 years. The median time to development of t-MDS/AML is 3 to 5 years, with the risk decreasing markedly after the first decade.

• Distinctly different from MDS/ AML De Novo with worse prognosis

  * Therapy-related myelodysplasia and acute myeloid leukemia
  * doi: 10.1053/j.seminoncol.2013.09.013
Immunotherapy side effects – The “-itises”

• According to the NCCN guidelines* the potential immune related conditions are:

  - Myocarditis, dermatitis, pruritis, hyperglycemia related DKA, asymptomatic/subclinical hypothyroidism, overt hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, colitis, pancreatitis, transaminitis, inflammatory arthritis, myositis, polymyalgia rheumatica and giant cell arteritis, aseptic meningitis, Guillain-Barre, myasthenia Gravis, peripheral neuropathy, transverse myelitis, vision changes, pneumonitis and acute kidney injury

• Not mentioned in the guidelines – infusion reactions (not as common as with conventional chemo)
Targeted Therapy – side effects of VEGF inhibition

• Read package insert to identify specific target

• Research the target in terms of pathology of overexpression and the physiology/ side effects of inhibition

• VEGF is responsible for neovascularization, wound healing, secretion of nitrous oxide (vasodilation and naturesis)

• Can’t do surgery if on this ~6 weeks?? (institution standards), impaired wound healing

• hypertension (most common side effect), thyroid dysfunction, colitis, nephritis
Primary Cancer Related Sequelae

• Many patients may never be symptomatic (at least initially) from their cancers. For example, many cancers found on screening, lab review, and/or physical exam.

• Cancer related pain, mechanical effects of tumor (i.e. hydrenephrosis, urethral obstruction, skin breakdown), physiologic effects of tumor (thermoregulation, dyspnea, malabsorption), emotional impact, inability to work, decreased performance status, change in appearance.

• Is disease and/or disease progression causing sequelae or is it the treatment?
Common Terminology Criteria for Adverse Events

- Current version 5.0 published Nov 2017 by US Dept of Health and Human Service (155 page document)
- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Side Effects

- What is the difference between:
  - Diarrhea from chemo versus immune therapy versus targeted therapy?
  - Pneumonitis caused by bleomycin versus immunotherapy?
  - Skin changes from chemo versus immunotherapy?
  - Transaminase increase from chemo versus immunotherapy?
  - Thyroid dysfunction with immunotherapy versus target therapy (i.e. VEGF inhibitor)?
NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities

• Provides guidance on pre-therapy assessment, monitoring frequency for possible toxicities and evaluation for abnormal findings.

• Current guidelines by NCCN is version 4.2021 (104 page document)
Dermatologic Adverse Events – Maculopapular Rash

- **G1** Continue treatment, topical emollient, antihistamine for sx

- **G2** Continue treatment, topical emollient, antihistamine for sx, moderate to high potency topical steroids. If unresponsive to topical consider prednisone 0.5 mg/kg/day – taper length not mentioned

- **G3-4** Hold treatment, high potency topical steroids, prednisone 0.5 – 2 mg/kg/day until Gr 1 then taper over 4-6 weeks, urgent derm consult

- **Clinical Pearl**: If you are not familiar/comfortable with high dose steroid tapers discuss this with BMT colleagues. Many providers consult endocrine for taper management.

- **Consider** TMP/SMX prophylaxis. For Gr2 reassess weekly.

Case Study

• 69 male born in India with metastatic bladder cancer s/p MVAC with progression.
• Pembrolizumab 6/2020 – 1/21/2021 then progression on scans but had G1 rash starting in 1/2021. Pt placed on emollients and hydroxyzine then progressed to G2 – added triamcinolone and ultimately a methylprednisolone dose pack x2
• Started enfortumab 3/18/21 when rash was at G1. By 4/13/21 rash progressed quickly to Gr 3 after 3rd dose with almost 100% BSA, severe pruritis and desquamation. I added prednisone 1 mg/ kg with prophylactic TMP/SMX. Treatment held and then resumed 5/20/21
• Gr 3 rash returned by 6/3 after second dose. Repeated steroid taper. D/C treatment
• Started Sacituzumab 7/22/2021 – G1 rash persists and is treated supportively
• Pt has limited treatment options.
Hypothyroidism

• If asymptomatic/subclinical monitor TSH, free T4 Q 4-6 weeks or each cycle
• Subclinical hypothyroidism = elevated TSH with normal T4
• If elevated TSH (>10) with normal free T4 continue immunotherapy, consider levothyroxine
• Clinical (overt) Hypothyroidism – Continue treatment. Consider endocrine Consult. Initiate levothyroxine therapy (1.6 mcg/kg/day – with consideration of comorbid conditions. Always safer to dose lower.

• Guidelines recommend TSH monitoring Q 4-6 weeks to guide adjustments

• Consider waiting 10 weeks for adjustments

Diarrhea/ Colitis

• Consider the timeframe from treatment start and trend

• Clinical Pearl – Review patient diet!

• Use CTCAE grading

• Initial assessment – stool testing: C.Diff, O & P, etc then supportive care

• OTC label on loperamide is different then Rx dosing. Use the correct dosing

• Adding diphenoxylate/ atropine or tincture of opium. Need DEA license to Rx
Diarrhea/ Colitis continued

- The incidence of grade 3 and 4 colitis was 9.1% with CTLA-4 monotherapy, 1.3% with PD-1/L1 therapy, and 13.6% with combination therapy [1]

- Fecal calprotectin and lactoferrin are used to dx IBD in general population. If positive while using immunotherapy research shows high likelihood (up to 90%) of involvement with histologic inflammation and/or ulcers [2]


Diarrhea/ Colitis continued

- G1- Consider holding immunotherapy. Add loperamide or diphenoxalate/atropine x 2-3 days. Supportive care. If progressive check lactoferrin/calprotectin → if positive treat as Gr 2.

- G2 Hold immunotherapy. Start prednisone 1-2 mg/kg/day. If no response consider infliximab or vedolizumab. GI Consult

- G3 Same as G2 then discontinue anti-CTLA-4: consider resuming anti PD1/ PDL-1 after resolution of toxicity

- G4 Same as G2. Permanently discontinue immunotherapy agent responsible for toxicity. Inpatient care. IV methylprednisolone 1-2mg/kg/day. If no response continue steroids and consider infliximab or vedolizumab
Diarrhea/ Colitis continued

- How do you know the agent responsible if there is more than one agent? i.e. ipilimumab/ nivolumab, pembrolizumab and lenvatinib, nivolumab and sunitinib
- Acute sx most likely not due to either agent. Review Diet!
- With immunotherapy sx usually come on slowly over weeks and then progress. Read package inserts for timing/ onset data. With ipilimumab /nivolumab d/c ipilimumab first if Gr2. If sx resolve then proceed with reduced dose ipilimumab. No resolution hold nivolumab and follow guidelines.
- With immunotherapy and VEGF agent (i.e. pembrolizumab/lenvatinib or nivolumab/ sunitinib) hold the VEGF agent as this is a daily med. If diarrhea resolves proceed with dose reduction per package insert. If no response then treat as Gr2 per guidelines. There is no reduction in immunotherapy. If progression of diarrhea then will need to D/C
Transaminitis

- Will be asymptomatic. Found with routine monitoring.
- Consider other etiologies: viral, mets, medications, CBD, supplements
- G1 < 3X ULN Increase frequency of monitoring
- G2 3-5X ULN. Hold immunotherapy. Monitor labs Q 3-5 days. Consider prednisone 0.5 – 1 mg/kg/day
- G3 >5-20X ULN. Hold immunotherapy. Prednisone 1-2 mg/kg/day. Consider inpatient care with daily LFTs. If steroid refractory consider mycofenolate. Hepatology consult
- G4 > 20X ULN Permanently discontinue. Hospitalized Pt. Beyond the scope of this talk
Transaminitis continued

- With immunotherapy sx usually come on slowly over weeks and then progress. Read package inserts for timing/onset data. With ipilimumab/nivolumab d/c ipilimumab first if Gr2. If sx resolve then proceed with reduced dose ipilimumab. No resolution hold nivolumab and follow guidelines.

- With immunotherapy and VEGF agent (i.e. pembrolizumab/lenvatinib or nivolumab/sunitinib) hold the VEGF agent as this is a daily med. If diarrhea resolves proceed with dose reduction per package insert. If no response then treat as Gr2 per guidelines.
Clinical Pearls for Practice

• Understand the physiology
• Understand CTCAEs – You should be able to manage all G1 and G2 yourself
• Steroid refractory patients require specialist intervention and likely hospitalization
• Know the guidelines for dose modifications
• Review package inserts
• Know your supportive care drugs and have resources at arms’ length!
Thank You!
References

• Up to Date


References


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• Therapy-related myelodysplasia and acute myeloid leukemia


• doi: 10.1053/j.seminoncol.2013.09.013
References


- NCCN Common Terminology Criteria for Adverse Events (CTCAE) v5.0
