Management of Toxicities of the New Oncologic Agents

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I have no real or apparent conflict of interest with the information presented in this lecture.
Objectives

- Recognize the new oncologic agents used in the treatment of cancer
- Identify common side effects and toxicities related to the newer oncologic agents
- Develop management strategies to address these side effects and toxicities in the hospitalized oncology patient
# Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B-cell lymphomas and leukemias</td>
<td>CRS Immunodeficiency</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td></td>
<td></td>
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<tr>
<td>Obinituzumab</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Breast cancer</td>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
<td>Diarrhea Exanthema</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Colorectal cancer, Breast cancer, Renal cell cancer, NSCLC</td>
<td>Hypertension, GI bleeding or perforation, Thromboembolism</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>VEGFR</td>
<td>Gastric cancer</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>Target</td>
<td>Indications</td>
<td>Toxicities</td>
</tr>
<tr>
<td>-------------</td>
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<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Imatinib</td>
<td>BCR-ABL</td>
<td>CML</td>
<td>Pleural/pericardial effusion, Pulmonary Hypertension</td>
</tr>
<tr>
<td>Dasatinib</td>
<td></td>
<td>ALL</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Ponatinib</td>
<td></td>
<td>NSCLC, Pancreatic cancer</td>
<td>Exanthema, diarrhea, GI bleeding or perforation</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>NSCLC</td>
<td></td>
</tr>
<tr>
<td>Idelalisib</td>
<td>PI3K</td>
<td>B-cell lymphoma</td>
<td>Pneumonitis, Colitis, hepatosis</td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEK</td>
<td>Melanoma</td>
<td>Diarrhea, edema, Decreased LVEF</td>
</tr>
</tbody>
</table>
## Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afliberecept</td>
<td>VEGF</td>
<td>Colorectal cancer</td>
<td>Hypertension, GI bleeding or perforation, Thromboembolism, PRES</td>
</tr>
<tr>
<td>Axinitinb</td>
<td>VEGFR</td>
<td>Renal cell cancer</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>Renal cell carcinoma, Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multiple kinases</td>
<td>Renal cell carcinoma</td>
<td>Decreased LVEF, Hypertension</td>
</tr>
<tr>
<td>Pazopanib</td>
<td></td>
<td>Soft tissue sarcoma, Renal cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>
# Bispecific Antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>CD3/CD19</td>
<td>ALL, B-cell lymphomas</td>
<td>CRS, Neurotoxicity (seizures), Transaminitis</td>
</tr>
</tbody>
</table>
# Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, Renal cell cancer, Hodgkin’s lymphoma</td>
<td>Immune-related adverse events:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Diarrhea, colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypophysitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Immunohepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Polyarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Neurological</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Urothelial cancer, NSCLC</td>
<td></td>
</tr>
<tr>
<td>Avelumab</td>
<td></td>
<td>Merkel cell cancer</td>
<td></td>
</tr>
</tbody>
</table>
## Cellular Treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T cells</td>
<td>CD-19</td>
<td>ALL B-cell lymphomas</td>
<td>CRS Neurotoxicity (seizures, encephalopathy, ischemia)</td>
</tr>
</tbody>
</table>
Cytokine Release Syndrome (CRS)

- Potentially life-threatening systemic inflammatory reaction seen after infusion of agents that target immune effector sites
- Events usually occur during or after first exposure to a new agent
- Driven by an increase of inflammatory cytokines which are released after the activation and cytotoxic damage of monocytes, macrophages, and different lymphocyte populations
- High levels of interleukin (IL)-6 have a central role
Cytokine Release Syndrome (CRS)

<table>
<thead>
<tr>
<th>Main Symptoms of Cytokine-Release Syndrome</th>
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</thead>
<tbody>
<tr>
<td>Constitutional</td>
</tr>
<tr>
<td>Fever, chills, headache, asthenia, myalgia, arthralgia, back or abdominal pain</td>
</tr>
<tr>
<td>Organ related</td>
</tr>
<tr>
<td>Oliguria, bronchospasm, dyspnea, hypotension, tachycardia, arrhythmia, confusion, erythema, urticarial reaction, pruritus</td>
</tr>
<tr>
<td>Lab tests</td>
</tr>
<tr>
<td>Hypokalemia, ↑BUN, ↓GFR, abnormal blood counts and/or coagulation tests, ↑CRP and/or ↑procalcitonin</td>
</tr>
</tbody>
</table>
Cytokine Release Syndrome (CRS)

- **Management**
  - The majority of events after the administration of monoclonal antibodies can be managed by antipyretics, antihistamines, corticosteroids, adequate fluid load, cardiopulmonary monitoring, and oxygen supplementation.
  - Rarely patients need to be admitted to the ICU for vasopressor support or hemofiltration.
Cytokine Release Syndrome (CRS)

- CAR T cell therapy
  - Grade ≥3 fever, hypotension, or hypoxia was reported in up to 80%, 40%, and 15% of treated patients, respectively in a recent study of toxicities (Brudno JN, Kochenderfer JN.. Blood. 2016;127(26):3321–30)
  - May affect the kidneys, liver, central nervous system (CNS), GI, and musculoskeletal system
  - Monoclonal antibodies against IL-6 receptors (tocilizumab)
    - Due to its high cost, as well as potential severe adverse events, including infections, reactivation of viruses, or tuberculosis and hepatotoxicity, treatment using tocilizumab should be limited strictly to critically ill patients
Central Nervous System Events

- Can occur with BABs and CAR T cells
- May happen at any time during CRS or as a singular complication
- May potentially necessitate intubation and mechanical ventilation for airway protection, as well as antiepileptic therapy in patients with seizures
>50% who received blinatumomab in a phase 2 trial for acute B-lymphoblastic leukemia experienced neurologic events such as tremor, encephalopathy, cerebellar alteration, or seizures (Topp MS, et al. *Lancet Oncol.* 2015;16(1):57–66)

13% classified as severe or life-threatening

Grade ≥3 neurotoxicity was reported in 13 of 27 patients in an early clinical trial with acute lymphoblastic leukemia patients undergoing CAR T-cell therapy (Turtle CJ, et al. *Blood.* 2015;126:3773)

The pathophysiology of these neurotoxic effects is still unclear but, as in CRS, inflammatory cytokines seem to be involved
Central Nervous System Events

- Differential Diagnosis...
  - Encephalitis due to herpes virus species
  - Focal infections such as toxoplasmosis
  - Primary CNS hemorrhage due to altered coagulation cascade
  - Clotting in CNS vasculature due to thrombophilia and secondary hemorrhage
Central Nervous System Events

Management

Dexamethasone

Problem: steroids interfere with immune effects of treatment and may have a negative impact on tumor response!

Anticonvulsants if seizures, prophylactic in patients who may be at increased risk
Immune-Related Adverse Events (IRAEs)

- Affected agents
  - Checkpoint inhibitors (CTLA-4, PD-1/PD-L1, PD-2/PD-L2)
  - Work by inhibiting the inhibitory signals sent from the cancer to T-cells
  - **Problem**: agents can attenuate tolerance and cause overwhelming inflammation, tissue damage, and autoimmunity
  - 85% (ipilimumab), 70% (PD-1/PD-L1)
Immune-Related Adverse Events (IRAEs)

- Main target tissues
  - GI tract - most symptoms start 6 or more weeks after initiation of treatment
  - Diarrhea
  - Enterocolitis
  - Perforation (rare)
  - May require ICU admission
Immune-Related Adverse Events (IRAEs)

- Main target tissues
  - Liver - not usually seen prior to 6 weeks after start of therapy
  - Transaminitis
  - Jaundice

- Etiology unclear, however cyclosporine has been reported to be effective in reversing severe liver toxicity (Huffman, BM, et al.)

Immune-Related Adverse Events (IRAEs)

- Main target tissues
  - Skin - seen in more than 1/3 of all patients; usually self-limiting and manageable with conventional agents (Sibaud V, *Am J Clin Dermatol*. 2017 Dec 18.)
  - Maculopapular rash (eczema-like spongiotic dermatitis)
  - Pruritis
  - Vitiligo-like lesions
  - Autoimmune skin disease (bullous pemphigoid, dermatomyositis, alopecia)
  - Sarcoidosis
Immune-Related Adverse Events (IRAEs)

- Main target tissues
  - Endocrine system - symptoms usually appear 9 or more weeks after initiation of treatment
    - Hypophysitis
    - Thyroiditis
  - More common with ipilimumab than PD-1/PD-L1 agents
Interstitial Pneumonia and Pneumonitis

- *Pneumocystis jirovecii* and *Cytomegalovirus* are the main infectious agents for pneumonia in immunocompromised patients

- **Risk Factors**
  - Lymphoproliferative malignancies
  - Long-term use of glucocorticoids
  - Lymphocytopenia (CD4 < 200/μL)
  - Allogeneic hematopoietic stem cell transplantation
Interstitial Pneumonia and Pneumonitis


- High-dose cotrimoxazole (90–120 mg/kg/day, intravenously over ≥14 days) is treatment of choice for first-line therapy

- An oral route from the beginning is an option only in stable patients with mild disease

- Pentamidine (4 mg/kg/d i.v.) or the combination of primaquine (30 mg/d) and clindamycin (600 mg/d x 3) can be considered in patients with contraindications to, or relapsing after, cotrimoxazole
Interstitial Pneumonia and Pneumonitis

- Drug-induced (non-infectious) pneumonitis
  - Rituximab - 3-5%, mild
  - Dasatinib (TKI) in about 28%; mild
  - Idelalisib (PI3K-i) 10-20%; usually mild, but isolated severe pneumonitis and death have been reported
  - Checkpoint inhibitors - 3-6%; mostly mild
  - Steroids can help in moderate-severe cases; mild cases may be more limited and managed conservatively
Events Associated With Impaired Angiogenesis

- Arterial thromboembolism
  - Bevacizumab
    - 1% in breast cancer
    - 11.3% in lung cancer
Events Associated With Impaired Angiogenesis

- Hypertension
  - Bevacizumab
  - Dasatinib (pulmonary)
- Cardiac (\(\downarrow\)LVEF, CHF)
  - Bevacizumab
  - Sorafenib
  - Sunitinib

- GI catastrophic events (hemorrhage, perforation)
  - Bevacizumab (RR \(\approx\) 2.5-4.0)
Other Toxicities

- Newer agents are less toxic than cytotoxic chemotherapy, but they are present nevertheless.
- Usually present in normal tissues affected by the agents.
Toxicities of the Newer Agents

- EGFR inhibitors - remember the “E” stands for epidermal, so skin toxicity is the major feature
  - Maculopapular rash
  - Resembles acne
Toxicities of the Newer Agents

- **EGFR inhibitors**
- **Mild rash** often associated with response to dose (“we’re giving enough”)
- **Starts 2-4 weeks after initiation of therapy, peaks at 2-4 months, then usually regresses over time**
Toxicities of the Newer Agents

- *BRAF* inhibitors
  - Squamous cell carcinomas and keratoacanthomas (19-26%)
  - May develop within weeks of starting therapy
  - Due to paradoxical activation of the mitogen activated protein kinase (MAP kinase) pathway that bypasses the inhibition of *BRAF*
- Surgical excision
- Does not require discontinuation of therapy
Toxicities of the Newer Agents

- **BRAF** inhibitors

  - One reported case of rapid progression of CMML

  - Other cutaneous toxicities (rash, photosensitivity reactions, alopecia) as with EGFR inhibitors

  - QT prolongation (vemurafenib, due to CYP3A4 effects)

  - Fever (dabrafenib, 28% of patients, may require discontinuation)

  - Hyperglycemia (dabrafenib, 6% of patients, may require discontinuation)
Toxicities of the Newer Agents

- Monoclonal antibodies
- Fever, chills, back pain, wheezing
- Treated by premedication
- Reactivation of Hepatitis B virus and progressive multifocal leukoencephalopathy
Toxicities of the Newer Agents

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation [see Warnings and Precautions (5.1)].

- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA [see Warnings and Precautions (5.2)].
Human Antibody Infusion Reactions

- Occurs with humanized antibody agents directed at targets on cancer cells
  - Rituximab (Rituxan®)
  - Trastuzumab (Herceptin®)
  - Ofatumumab (Arzerra®)
  - Bevacizumab (Avastin®)
- Essentially…any drug whose name ends in “…mab” which means monoclonal antibody
Human Antibody Infusion Reactions

- Features
  - Fever
  - Chills
  - Nausea
  - Wheezing
  - Back pain

- Lab features
  - ↑ AST/ALT
  - Thrombocytopenia
  - ↑ PT
Human Antibody Infusion Reactions

- **Management**
  - Premedicate: acetaminophen, diphenhydramine, steroids (optional)
  - If reaction occurs…
    - Stop infusion
    - Administer (re-administer) above agents, re-start infusion at 50% initial infusion rate when symptoms resolve
Extravasation

- Spectrum of problems variable, from minor irritation to skin necrosis, ulceration, nerve damage, loss of limbs
- Most commonly occurs with agents known as vesicants
  - Alkylating agents: mechlorethamine, cisplatin, mitomycin C
  - DNA intercalating agents: doxorubicin, daunorubicin
  - Plant alkaloids: vincristine, vinblastine, vinorelbine
Extravasation

- Management…prevention is the goal!
  - Monitor IV infusions carefully, patient/nurse should have low threshold for calling attention to symptoms of pain or swelling at the infusion site, redness
  - Place PICC line or CVC in those patients who will receive high risk agents
Extravasation

- Management...prevention is the goal!
  - Immediately stop any infusion in question
  - Apply cold compresses to area (warm compress with plant alkaloids)
  - Topical DMSO 50% solution 1.5 ml q 6° x 7-14 days can relieve extravasations from mitomycin C and the anthracyclines
Extravasation

- Management…prevention is the goal!
- Hyaluronidase 150 U in 1-3cc saline injected around site can alleviate extravasations from plant alkaloids and etoposide
- Sodium thiosulfate 0.17-mmo/L solution can be injected into mechlorethamine extravasations, may also be effective in cisplatin, carboplatin, cyclophosphamide, dacarbazine, and oxaliplatin
- If local measures fail, plastic surgeon consultation initiated
Extravasation

- Management...prevention is the goal!
- Recall reaction: reappearance of ulcers or burns in areas previously extravasated by the same chemotherapy
- “Extravasation kit” with necessary products should be available in all chemotherapy administration areas, along with a listing of antidotes for each agent