46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Cidara Therapeutics**
- **Employment: Sfunga Therapeutics**
- **Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics**

Goals of This Review

- Focus on testable complications specific to the immunocompromised host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Fundamentals: Underlying disease risks

- Immune defects associated with underlying malignancy (and prior therapies)
  - AML and myelodysplastic syndromes (MDS)
    - Qualitative and quantitative neutropenia
  - Lymphoma
    - Functional asplenia
  - CLL and multiple myeloma
    - Hypogammaglobulinemia
  - Aplastic anemia
    - Severe, prolonged neutropenia

Fundamentals: Therapeutic risks

- Recognize risks with cytotoxic therapy (neutropenia)
  - Prolonged (>10 days) and profound (< 500 cells / mm3) leads to high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
    - Outcomes tend to be poor – preventative therapies important
- Recognize infectious risks with other biologic therapies that immunosuppress
  - T cell suppressing agents and 'targeted' biologics
    - Viral and fungal infections

Immune modulating anti-cancer drugs

- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

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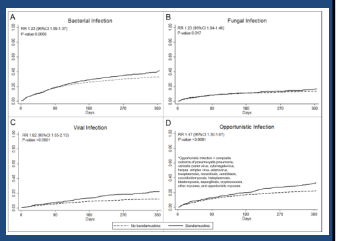
Bendamustine

- Nitrogen-based alkylating agent and antimetabolite
- Indolent non-Hodgkins lymphomas, CLL
- Neutropenia *and lymphopenia* (months - years)
- Higher risks for infections (bacterial, CMV, PJP, histoplasmosis)



Fung et al. Clin Infect Dis 68(2): 247-55

Biological Therapies

- Generally broken into three categories
  - Biological response modifiers. Exert effects by stimulating immune system (ex. CSFs)
  - Gene therapies
  - Targeted therapies (mAbs and small molecule enzyme inhibitors)

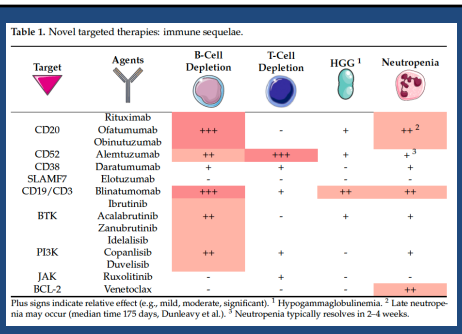


Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Plus signs indicate relative effect (e.g., mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–4 weeks.

Little et al. J Fungi 7, 1058

Key anti-CD Monoclonal Abs

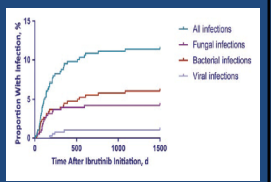
- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
    - B cell depletion: CLL, lymphoma
    - Prolonged B cell (6 – 9 mo.); neutropenia can occur
    - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML, PJP
  - Alemtuzimab (anti-CD52)
    - T and B cell depletion for a long time (about 6 months): lymphoma, leukemia, BMT (graft vs. host disease treatment)
    - Herpes viruses (esp. CMV), fungal infections (PJP, Aspergillus)

Tyrosine kinase inhibitors

- BCR – ABL Tyrosine – kinase inhibitors
  - Inhibit signal transduction through BCR-ABL oncogene (ex. imatinib, dasatinib, nilotinib)
    - CML. Think T and B cells (VZV, Hep B reactivation)
    - Autoimmune pneumonitis and colitis (infection mimic), steroids
    - Aspergillosis and other IFI

Bruton's tyrosine kinase inhibitors

- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections
  - Aspergillosis (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018 132(18): 1985-88
Blez et al. Haematologica 2019 (in press)

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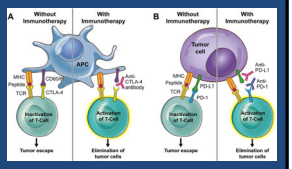
Phosphoinositide 3-kinase (PI3K) inhibitors

- Selective small molecule inhibitors of the B-cell receptor pathway (idelalisib)
- Decreased T-reg, inhibition NK, neutropenia
- Possibly increased IFI (esp. with combo)
- NBV screening, consider antiviral prophylaxis in HBsAg negative or anti HBc-positive patients

Maschmeyer et al. Leukemia 33, 844-62 (2019)

Checkpoint inhibitors

- Block immune checkpoints that regulate T cell activation / function – multiple tumors
- Targeting PD-1 on T cells (pembrolizumab, nivolumab, cemiplimab) or PD-L1 on tumor cells (atezolizumab, avelumab, durvalumab)
- Targeting CTLA-4 on T cells (ipilumumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above



Soularue et al. BMJ gut 2018

JAK inhibitors

- Janus kinase inhibitor (Ruxolitinib)
- Inhibit DC, CD4+ fx, decreased T-reg, NK
- HBV: screening, prophylactic entecavir in HBsAg - / anti-HBc-positive
- Tb screening

Maschmeyer et al. Leukemia 33, 844-62 (2019)

Venetoclax

- Inhibits anti-apoptotic BCL2 – family proteins (AML, lymphoid malignancies)
- Sometimes given with hypomethylating agents for AML (ex. azacytidine)
  - Severe, prolonged neutropenia – bacterial, fungal infections
  - Drug interactions may limit use of azole prophylaxis
    - Cyp3a inhibition requires VEN dose decrease / toxicities
    - Aspergillosis increasingly recognized

Neutropenic "syndromes"

Question #1

35 year old woman with AML day 15 after induction therapy.
Fever, chills, diffuse erythematous rash. Blood culture + GPC in chains
Exam – 100/62, HR 120, grade 2 oral mucositis, and a diffuse, blanching, erythematous rash. CXR - bilateral diffuse infiltrates. She is receiving levofloxacin and acyclovir.
This is most consistent with infection with which of the following organisms?

A. *Streptococcus pneumoniae*
B. Coagulase-negative *Staphylococcus*
C. *Enterococcus faecalis*
D. *Streptococcus mitis*
E. *Stomatococcus mucilaginosus*

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Viridans Streptococci

- Key points: neutropenia, mucositis, high-dose cytosine arabinoside, fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- VGS shock syndrome:
  - After 24-48 hours, hypotension in 1/3 of cases
  - Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- *S. mitis*, *S. oralis*
- Vancomycin
- Mortality high (15-20%)

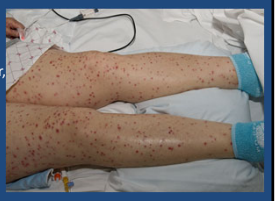
Testable contexts: Breakthrough Bloodstream Infections

- Typical patient- neutropenic, progressive sepsis
- Recognize holes in protection, specific syndromes
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → Stenotrophomonas, ESBL
  - Sepsis with carbepenems → KPC
  - Lung and skin lesions → *P. aeruginosa*, Fungi
  - Skin lesions, gram + → *Corynebacterium jeikeium*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp., Stomatococcus mucilaginosis*

Question #2

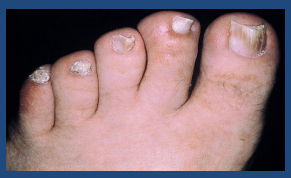
59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender, with no central ulceration.

A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*



Fusarium

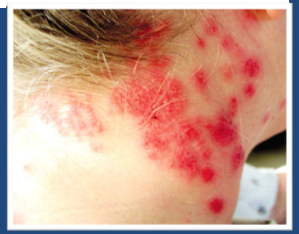
- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis



Question #3

50-year-old woman with newly diagnosed AML developed tender, pruritic papules and plaques on her neck. She had been febrile 38.7°C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC). Most likely etiology:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster Virus
E. *Pseudomonas aeruginosa*



Haverstock, C. et al. Arch Dermatol 2006;142:235-b-240-b.

Sweet's syndrome

- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated, drug induced
- Tender erythematous plaques and nodules typical; also bullous, cellulitic, necrotizing lesions
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures - negative
- Steroids

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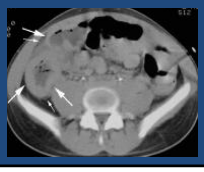
Question #4

70 yr old woman with AML, neutropenic for 15 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain. Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Levofloxacin and fluconazole prophylaxis. 4 days prior to her admission for chemotherapy, she ate Chinese food with fried rice.

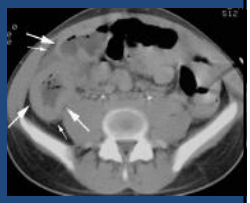
Which is the most likely etiology?

A. Norovirus
B. *Clostridioides (Clostridium) difficile*
C. Mixed anaerobic and aerobic bacteria
D. *Candida albicans*
E. *Bacillus cereus*



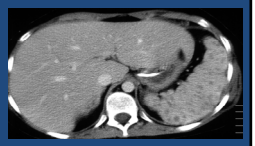
Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
  - Can be accompanied by bacteremia
    - Hint: mixed, anaerobic (*C. septicum, C. tertium, B. cereus)*
  - Medical and (less often) surgical management



Hepatosplenic Candidiasis

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain
- Differential: other fungi, bacteria, lymphoma
- *C. albicans* most common
  - Amphotericin B primary therapy followed by prolonged fluconazole, echinocandins



Summary: PEARLS

- Recognize typical infections associated with neutropenia and/or other immune suppression (biologic inhibitors of cellular defenses)
- Predict breakthrough bloodstream pathogens based on therapy
- Know specific syndromes
  - *S. viridans* sepsis – ARDS
  - Differential of skin lesions
  - Neutropenic patients - IFI
    - Pulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - GI tract enterocolitis

Thank you

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