

56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD



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, Merck and Company, Sfunga Therapeutics
- Ownership Interests: MycoMed Technologies

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

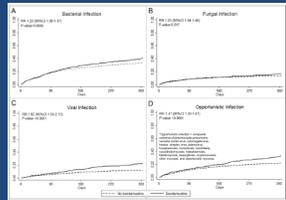
- Drugs that impact neutrophils
 - Many cytotoxic agents
 - Bacterial infections, fungal infections
- Drugs that impact T cells
 - Purine analogs (fludarabine, cladribine, clofarabine) and temozolomide
 - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

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Bendamustine

- Nitrogen-based alkylating 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)

For a robust review

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Target molecule	Agents available
CD20	Rituximab, obinutuzumab, epratuzumab, ocaratuzumab
CD22	Epratuzumab
CD25	Urelizumab
CD27	Urelizumab, epratuzumab, hertofumab
CD30	Urelizumab
CD38	Urelizumab
CD40	Urelizumab
CD45	Urelizumab
CD52	Alemtuzumab
CD54	Urelizumab
CD56	Urelizumab
CD59	Urelizumab
CD63	Urelizumab
CD68	Urelizumab
CD70	Urelizumab
CD73	Urelizumab
CD74	Urelizumab
CD77	Urelizumab
CD80	Urelizumab
CD86	Urelizumab
CD137	Urelizumab
CD137L	Urelizumab
CD138	Urelizumab
CD147	Urelizumab
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Supplement in Clin Microbiol and Infect 24, 2018

Key anti-CD Monoclonal Abs

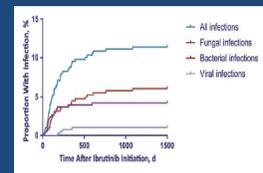
- Common antibodies that impact B and T cells
 - Rituximab (anti-CD20)
 - B cells: CLL, lymphoma
 - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML
 - Alemtuzimab (anti-CD52)
 - T and B cell depletion for a long time (about 6 months): lymphoma, 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)
 - Aspergillus 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
 - Aspergillus (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



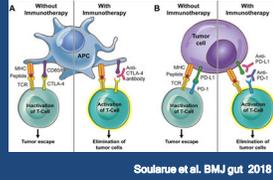
Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018; 132(18): 1985-88
Blasz et al. Haematologica 2019 (in press)

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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 (ipilimumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF- α targeting agents for above



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 \pm 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?

- Streptococcus pneumoniae*
- Coagulase-negative *Staphylococcus*
- Enterococcus faecalis*
- Streptococcus mitis*
- Stomatococcus mucilaginosus*

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 \rightarrow viridans Streptococci
 - Sepsis with β -lactams \rightarrow *Stenotrophomonas*, ESBL
 - Sepsis with carbapenems \rightarrow KPC
 - Lung and skin lesions \rightarrow *P. aeruginosa*, Fungi
 - Skin lesions, gram + \rightarrow *Corynebacterium jeikeium*
 - Mucositis (upper, lower tract) \rightarrow *Fusobacterium* spp., *Clostridium* spp., *Stomatococcus mucilaginosus*

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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*



Skin Lesions

- Candidiasis
 - Small, tender papules
- Herpes
 - vesicular
- *Aspergillus*
 - ulcerative, necrotic
- Other filamentous fungi (*Fusarium*, *P. boydii*)
 - Multiple, erythematous, different stages
- *P. aeruginosa*
 - Ecthyma gangrenosum



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

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*



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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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