CANCER RELATED INFECTION AND USE OF COLONY STIMULATING FACTORS

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Learning Objectives

☐ Summarize national guidelines for risk assessment and prevention of febrile neutropenia.

☐ Given patient case information, evaluate the patient’s risk for developing febrile neutropenia.

☐ Given patient case information, recommend a prophylactic drug regimen to prevent febrile neutropenia.

☐ Describe treatment options for a patient who develops febrile neutropenia.
Introduction

- Chemotherapy-induced neutropenia (CIN)
  - Major dose-limiting toxicity of systemic cancer chemotherapy
  - Increases risk of infection, prompts dose delays/reductions, impacts effectiveness and impairs quality of life

Introduction

- Febrile neutropenia (FN)
  - Oncologic emergency
  - Often requires hospitalization and broad-spectrum antibiotic use
  - Associated with substantial morbidity, mortality, and cost

Definition of FN

- **Neutropenia**
  - Absolute neutrophil count (ANC) <500/mm³ or
  - ANC <1000/mm³ and a predicted decline to ≤500/mm³ over next 48 hours

- **Fever**
  - Single oral temperature ≥101°F (38.3°C) or 100.4°F (37.8°C) for ≥1 hour

NCCN Myeloid Growth Factors. v.1.2013
The Neutropenic Host

- Increased infectious risk
  - Decreased inflammatory response
  - Impaired bacterial defense
    - Disruption of integumentary and mucosal barriers
  - Microbial flora shifts due to severe illness and antibiotic usage

- Signs/symptoms of infection often absent
  - Fever is an early, nonspecific sign

The Neutropenic Host

- Frequency/Severity of Infection
  - Inversely proportional to ANC
  - Depth of neutropenia: <1000, <500, <100/mm3
  - Duration of neutropenia: >10 days
- Approximately 48%-60% of FN patients have infection
- 20% of patients with ANC <100/mm3 will develop a bloodstream infection

Occurrence of Neutropenic Events

- Historically, CIN has been considered a cumulative toxicity, with risk increasing over multiple chemotherapy cycles.

Occurrence of Neutropenic Events

- Recent data in different tumor types have shown that the greatest risk for CIN is in the first cycle.
  - In patients with breast cancer, most (67%) FN events in the initial placebo group occurred in the first chemotherapy cycle.
  - In patients with non-Hodgkin’s lymphoma, 50% of FN events occurred in the first chemotherapy cycle.

Consequences of FN

- FN occurs in 25%-40% of treatment-naïve patients treated with common chemotherapy regimens
- Approximately 50% of cancer patients receive <85% of their planned chemotherapy
  - Dose reductions/delays necessitated by CIN or FN

Consequences of FN

- Reductions in chemotherapy dose intensity result in compromised outcomes

- Healthcare implications
  - Mortality rate of 9.5% (hospitalized patients)
  - Mean length of stay: 11.5 days
  - Mean cost per FN episode: $19,110

Prevention of FN

- Dose reduction
- Different chemotherapy regimen
- Antibiotic prophylaxis
- Prophylactic colony-stimulating factors (CSFs)
  - Filgrastim (Neupogen®)
  - Pegfilgrastim (Neulasta®)
  - Sargramostim (Leukine®)
    - Not approved by FDA for prevention of chemotherapy-induced neutropenia
Antibiotic Prophylaxis

- Cochrane database review
  - Prophylactic antibiotics or CSFs for the prevention of infections and improvement in survival in cancer patients undergoing chemotherapy
  - Included two studies (195 patients)
  - Both studies showed a non-significant trend towards prevention of fever or hospitalization for FN in favor of antibiotic prophylaxis

Antibiotic Prophylaxis

- **EORTC Infectious Disease Group**
  - Caution should be used
  - Concerned about emergence of resistance

Colony-Stimulating Factors (CSF)

- Filgrastim, pegfilgrastim
  - ↓incidence of FN by 50%
  - ↓depth and duration of neutropenia
  - ↓FN-related hospitalizations and IV anti-infective use
  - ↓infection-related and all-cause mortality
  - ↑delivery of planned chemotherapy dose

Colony-Stimulating Factors (CSF)

- **Dosing**
  - Filgrastim – 5 mcg/kg subcutaneously daily x 7-10 days, begin 24-72 hr after chemotherapy
  - Pegfilgrastim – 6 mg (fixed) subcutaneously x 1 dose, given 24-72 hr after chemotherapy

Published Guidelines

- American Society of Clinical Oncology (ASCO)
  - ASCO Issues New Guideline on Fever and Neutropenia Management for Adult Patients with Cancer; Endorses International Pediatric Neutropenia Guideline
  - FOR IMMEDIATE RELEASE: January 14, 2013
    - www.asco.org

- National Comprehensive Cancer Network (NCCN)

- The European Organisation for Research and Treatment of Cancer (EORTC)

Published Guideline Terminology

- Primary prophylaxis
  - Administration of CSFs following the initial chemotherapy cycle in patients judged to be at an increased risk of developing FN
Published Guideline Terminology

- **Secondary prophylaxis**
  - Administration of CSFs following all subsequent chemotherapy cycles once a patient experiences:
    - a documented FN event
    - dose reduction/delay due to neutropenia
Risk Assessment: Criteria for Primary CSF Prophylaxis

- Assess frequency of FN associated with chemotherapy regimen
  - High risk >20%
  - Intermediate risk 10-20%
  - Low risk <10%
- Presence of additional patient risk factors
  - Patient-specific (age, comorbidities)
  - Disease-specific
- Treatment intent
  - Curative, non-curative, palliative

# Key Clinical Risk Factors for Developing FN

<table>
<thead>
<tr>
<th>Risk Related to</th>
<th>Association with Increased Risk of Developing FN</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>• Previous episode or FN history of severe neutropenia with similar chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• Type of chemotherapy or dose intensity &gt;80%</td>
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<tr>
<td></td>
<td>• Administration of combined radiotherapy</td>
</tr>
<tr>
<td></td>
<td>• Extensive prior treatment including large radiation port</td>
</tr>
<tr>
<td>Patient</td>
<td>• Age &gt; 65 years</td>
</tr>
<tr>
<td></td>
<td>• Poor performance status (ECOG ≥ 2)</td>
</tr>
<tr>
<td></td>
<td>• Poor nutritional status (e.g., low albumin)</td>
</tr>
<tr>
<td>Cancer</td>
<td>• Cytopenia due to bone marrow involvement of tumor</td>
</tr>
<tr>
<td></td>
<td>• Advanced or uncontrolled cancer</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>• Open wounds or active infection</td>
</tr>
<tr>
<td></td>
<td>• Serious comorbidities (e.g., COPD, liver disease, diabetes)</td>
</tr>
</tbody>
</table>
EORTC Patient Assessment Algorithm to Decide Prophylactic CSF Usage

- First Cycle Chemo High Risk >20%
  - Colony Stimulating Factors will be automatically ordered with first and subsequent cycles

- First Cycle Chemo Intermediate Risk 10 - 20%
  - Assess risk factors for increased febrile neutropenia (FN) risk
  - Increased FN risk?
    - yes\(^b\)
      - yes\(^b,c\)
        - no
        - yes\(^b,c\)
          - no
          - Observe patient and reassess at each cycle
    - no
      - Observe patient and reassess at next cycle

- Second or Subsequent Cycle Chemo
  - Febrile neutropenia event? Treatment delay or dose reduction due to neutropenia?
    - yes\(^b,c\)
      - no
      - Observe patient and reassess at each cycle
    - no
      - no

Pegfilgrastim 6mg given 24-72 hours post-chemo\(^d,e\)
<table>
<thead>
<tr>
<th>Disease State</th>
<th>High Risk Regimens &gt;20% FN Risk</th>
<th>Intermediate Risk Regimens 10-20% FN Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Cancer</td>
<td>MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)</td>
<td>carboplatin, gemcitabine</td>
</tr>
<tr>
<td></td>
<td>MVAC-Dose Dense (methotrexate, vinblastine, doxorubicin, cisplatin)</td>
<td>gemcitabine, cisplatin</td>
</tr>
</tbody>
</table>
| Breast Cancer      | AC→T-Dose Dense (doxorubicin, cyclophosphamide → paclitaxel)               | AC→T (doxorubicin, cyclophosphamide every 3 weeks)
|                    | AT (doxorubicin, docetaxel)                                               | paclitaxel every 3 weeks)               |
|                    | TAC (doxorubicin, cyclophosphamide, docetaxel)                             |                                          |
| Lung Cancer (non small-cell) | docetaxel                                                               |                                          |
| Lung Cancer (small-cell) | topotecan                                                                | docetaxel                                |
| Non-Hodgkin’s Lymphoma | CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for patients ≥ 65 years old  | CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for patients < 65 years old |
|                    | R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for patients ≥ 65 years old | R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for patients < 65 years old |
|                    | ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)              |                                          |
|                    | DHAP (dexamethasone, cisplatin, cytarabine)                               |                                          |
|                    | RICE (rituximab, etoposide, carboplatin, ifosfamide)                      |                                          |
|                    | ICE (ifosfamid, carboplatin, etoposide)                                   |                                          |
|                    | R-HYPERCVAD (rituximab, methotrexate, cytarabine, cyclophosphamide, vincristine, doxorubicin, dexamethasone, leucovorin) |                                          |
|                    | EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) |                                          |
| Ovarian Cancer     | topotecan                                                                 | EC (etoposide, cisplatin)               |
|                    | docetaxel                                                                 |                                          |
| Testicular Cancer  | VelIP (vinblastine, ifosfamide, cisplatin)                                |                                          |
|                    | BEP (bleomycin, etoposide, cisplatin)                                     |                                          |
|                    | IEP (ifosfamide, etoposide, cisplatin)                                    |                                          |
| Sarcoma            | MAID (doxorubicin, ifosfamide, dacarbazine)                               | dacarbazine, cisplatin, vinblastine     |
|                    | High Dose ifosfamide (>12 gm/m²)                                         |                                          |
|                    | AI (doxorubicin, ifosfamide)                                               |                                          |
| Melanoma           |                                                                            |                                          |

Approved by the Pharmacy and Therapeutics Executive Committee at The Ohio State University Medical Center. September 2006.
Summary of CSF Guidelines

- Recommendations for CSFs as primary and secondary prophylaxis are aligned across ASCO, NCCN, and EORTC guidelines

- Guidelines recommend evaluating patient risk factors and treatment intent, in addition to chemotherapy regimen risk in making decisions for CSF use in first and subsequent cycles (i.e., overall risk)

Aapro MS et al. 2011 Jan;47(1):8-32
NCCN Myeloid Growth Factors. v.1.2013
Summary of CSF Guidelines

- Primary prophylaxis (first and subsequent cycle use of CSFs) recommended for FN risk $\geq 20\%$ across the guidelines
- Consider primary prophylaxis if chemotherapy regimen has $10\%$-$20\%$ FN risk in presence of patient-specific risk factors or curative treatment intent

Aapro MS et al. 2011 Jan;47(1):8-32
NCCN Myeloid Growth Factors. v.1.2013
Role of the Pharmacist in the Prevention of FN

- Guideline development
- Risk assessment
- Multidisciplinary collaboration
- Staff education
- Patient education
- Outcomes monitoring
Why Develop Your Own Institutional CSF Guidelines?

- Improve patient outcomes
- Prevent hospital admissions
- Standardize care
- Increase staff awareness
Risk Assessment

Myelosuppressive chemotherapy → Neutropenia → Febrile Neutropenia → Complicated infection / sepsis → Prolonged hospitalization → Death

Pharmacist Intervention

Multidisciplinary Collaboration

- Discuss significance of patient risk factors with team
  - Especially important for intermediate-risk regimens
- Recommend CSFs as appropriate
  - Consider use in curative vs. non-curative setting (i.e., treatment expected to prolong survival or improve quality of life)
Staff & Patient Education

- **Staff education**
  - In-services/staff meetings
  - Pocket cards
  - Computer-based learning modules

- **Patient education**
  - Verbal and written education
  - Impact of dose intensity and on-time chemotherapy
  - Importance of receiving CSF injections
  - Adherence to fever guidelines and action plan
  - Importance of providing CSF injection information when giving medication history
Outcomes Monitoring

- Track compliance with guidelines
  - Initiation, risk factor assessment
- Patient outcomes
  - FN events, FN admissions, dose reductions/delays
- Insurance denials
Impact of Pharmacist Intervention at an NCCN University-Based Breast Cancer Clinic

- Retrospective evaluation of impact of prescriber education and pharmacist intervention on CSF use and guideline compliance

- Compared CSF use in two cohorts of patients with early-stage breast cancer (2003, n=49 vs. 2006, n=49) at substantial risk of developing FN

The likelihood of a patient experiencing ≥1 episode of FN was 80% lower in 2006 compared with 2003.

Abstract and poster.
LS is a 67-year-old woman recently diagnosed with early-stage breast cancer. Her tumor is 3.5 cm, high grade and has spread to her axillary lymph nodes.

LS has undergone surgery and presents to the outpatient oncology clinic to receive adjuvant chemotherapy with TAC for curative intent.

- Docetaxel 75 mg/m2, doxorubicin 50 mg/m2,
- Cyclophosphamide 500 mg/m2
- Administered every 21 days x 6 cycles
Patient Case

- PMH: type 2 diabetes mellitus, hypertension
- Social history: good performance status, lives and works with husband on dairy farm
- Medications:
  - glipizide 5 mg daily
  - lisinopril 20 mg daily
  - pioglitazone 30 mg daily
  - calcium 600 mg + vitamin D 400 units twice daily
- Labs:
  - WBC 8.5 x109/L, ANC 5.9 x109/L
  - CrCl 41 mL/min, total bilirubin 0.9 mg/dL
  - AST 29 u/L, ALT 36 u/L, alk phos 56 u/L, LVEF 52%
Patient Case Questions

- What risk factors does LS have for developing FN?
- Should LS receive primary prophylaxis with a CSF?
What risk factors does LS have for developing FN?

A. Age, malignancy type (breast cancer), hepatic dysfunction

B. Age, chemotherapy regimen, impaired renal function, diabetes (comorbidity)

C. Age, female gender, occupation (exposure to environmental pathogens), diabetes
Should LS receive primary prophylaxis with a CSF?

A. Yes
B. No
C. No, but she should receive secondary prophylaxis
## Overall Infection Risk in Cancer Patients

<table>
<thead>
<tr>
<th>Overall Infection Risk</th>
<th>Examples</th>
<th>Neutropenia &amp; Fever Risk Category</th>
</tr>
</thead>
</table>
| Low                    | • Standard chemotherapy for most solid tumors  
• Anticipated neutropenia <7 days  | Low |
| Intermediate           | • Autologous HSCT  
• Lymphoma  
• Multiple myeloma  
• Chronic lymphocytic leukemia  
• Purine analog therapy  
• Anticipated neutropenia 7-10 days  | Usually high  
(also factor in patient status) |
| High                   | • Allogeneic HSCT  
• Acute leukemia  
• Alemtuzumab therapy  
• GVHD treated with high dose steroids  
• Anticipated neutropenia >10 days  | Usually high, but variable depending on duration of neutropenia and immunosuppressive agents |

HSCT = hematopoietic stem cell transplant; GVHD = graft-versus-host disease

NCCN Prevention and Treatment of Cancer-Related Infections. v.1.2013
Evaluating the Patient with FN

- Site specific history/physical exam
  - Focus on common portals/sites
    - GI tract, skin, lungs, sinuses, groin, peri-rectal, peri-vaginal, vascular access devices

- Laboratory/radiology assessment
  - CBC, metabolic panel, liver function tests, pulsoximetry, chest radiograph

- Cultures
  - Blood, urine, other

Factors to Consider in Selecting Initial Empiric Therapy

- Most common organisms
- Potential sites of infection
- Local antimicrobial susceptibility patterns
- Broad spectrum of activity with antipseudomonal coverage
- Organ dysfunction
- Clinical instability (hypotension, sepsis)
- Recent antibiotic use
- Drug allergies
- Patient’s risk stratification

NCCN Prevention and Treatment of Cancer-Related Infections. v.1.2013
Most Common Pathogens

- Most common source of infection is patient’s own flora
- Historical
  - Pre-1960’s: majority Gram-negative organisms
  - 1970-forward: more Gram-positive organisms
    - Correlates with increased use of vascular access devices
- Gram-positive
  - Coagulase-negative staphylococci, S. aureus, viridans group streptococci, enterococci
- Gram-negative
  - E. coli, Klebsiella sp., Enterobacter sp., Pseudomonas
- Fungal, viral infections increase with duration of neutropenia
  - HSV, RSV, parainfluenza, influenza A and B are occasional initial pathogens

HSV = herpes simplex virus
RSV = respiratory syncytial virus

NCCN Prevention and Treatment of Cancer- Related Infections. v.1.2013,
## Risk Stratification in the FN Patient

<table>
<thead>
<tr>
<th>High-Risk Patient (if any factor listed below present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient status at time of FN</td>
</tr>
<tr>
<td>Substantial comorbidity</td>
</tr>
<tr>
<td>Clinically unstable</td>
</tr>
<tr>
<td>Anticipated prolonged neutropenia (ANC ≤ 100/mm³ and ≥ 7 days)</td>
</tr>
<tr>
<td>Hepatic insufficiency (transaminases &gt; 5x ULN)</td>
</tr>
<tr>
<td>Renal insufficiency (creatinine clearance ≤ 30 mL/min)</td>
</tr>
<tr>
<td>Complex infection, such as pneumonia</td>
</tr>
<tr>
<td>Alemtuzumab recipient</td>
</tr>
<tr>
<td>Grade 3 or 4 mucositis</td>
</tr>
</tbody>
</table>

NCCN Prevention and Treatment of Cancer-Related Infections. v.1.2013,
### Low-Risk Patient
(no high-risk features and most of the following)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient status</td>
<td>at time of development of FN</td>
</tr>
<tr>
<td>Acute comorbid illness</td>
<td>No associated acute comorbid illness that would necessitate inpatient treatment or close observation</td>
</tr>
<tr>
<td>Severe neutropenia</td>
<td>Anticipated short duration of severe neutropenia (ANC ≤ 100/mm³ and &lt; 7 days)</td>
</tr>
<tr>
<td>Performance status</td>
<td>Good performance status (ECOG 0 -1)</td>
</tr>
<tr>
<td>Hepatic or renal insufficiency</td>
<td>No hepatic or renal insufficiency</td>
</tr>
</tbody>
</table>

NCCN Prevention and Treatment of Cancer-Related Infections. v.1.2013,
Risk Stratification

Low Risk
- Hospital → IV therapy OR IV then PO therapy OR PO therapy
- Clinic OR home → IV at home OR PO therapy

High Risk
- Hospital AND IV therapy
Empiric Therapy: Vancomycin

- Should be considered in the following:
  - Clinically-apparent, serious, intravenous catheter-related infections
  - Bacteremia with Gram-positive bacteria (before final identification and susceptibility testing)
  - Known colonization with resistant pneumococci or methicillin-resistant Staphylococcus aureus
  - Hypotension or septic shock in a patient without an identified pathogen
  - Soft tissue infection

- Discontinue in 2-3 days if Gram-positive infection not identified and if clinically appropriate

NCCN Prevention and Treatment of Cancer-Related Infections. v.1.2013,
Persistent Fever

- Infection
  - Fever >3 days suggests non-bacterial
  - Drug resistance
- Inadequate drug coverage
- Drug fever
- Infection at avascular site (abscess, catheter)
- Not enough time
  - May take full 5 days to see results

Antifungal Therapy

- Studies indicate that up to 1/3 of FN patients on antibiotics >1 week have a fungal infection
  - Most cases caused by Candida or Aspergillus species
- Empiric antifungal therapy controversial
  - Most agree: patients who are febrile and severely neutropenic >5 days on antibiotics are candidates for antifungal therapy
- Use antifungal therapy earlier if indicated
  - CT indicative of invasive fungal infection
  - High clinical suspicion
  - History of invasive fungal infection

Antifungal Therapy - Agents

- Amphotericin B
  - Historical drug of choice
  - Broad spectrum
  - Toxicity → new formulations

- Azoles
  - Voriconazole, posaconazole
  - Broad spectrum, oral products
  - Drug interactions - inhibitor of cytochrome 3A4

- Echinocandins
  - Caspofungin, anidulafungin, micafungin
  - Broad spectrum, IV only
Use of CSF for FN

- CSFs not recommended for patients with neutropenia who are afebrile
- CSFs not recommended as adjunctive treatment with antibiotics for uncomplicated FN
- CSFs should be considered in FN patients who are high risk:
  - Prolonged (>10 days) and/or profound neutropenia (ANC <100/mm3), age >65 years, uncontrolled primary disease, pneumonia, sepsis syndrome, invasive fungal infection, or hospitalization at time of fever
- Consensus among NCCN, ASCO, and IDSA

NCCN Myeloid Growth Factors. v.1.2013
Role of the Pharmacist in the Treatment of FN

- Guideline development for treatment of FN
- Medication reconciliation
  - CSF administered?
- Antibiotic therapy
- Selection, dosing, administration, and monitoring
  - Data and culture review
  - Interventions for subsequent chemotherapy cycles
- Chemotherapy dose adjustment
- CSF use
- Communication with outpatient provider
LS receives her first cycle of TAC chemotherapy followed by pegfilgrastim 6 mg subcutaneously on day 2.

She calls the clinic 12 days later complaining of a fever this morning of 101.5°F, and she has a laceration on her lower leg from a work-related injury.

LS is instructed to come immediately to the hospital emergency department. Upon arrival, a CBC reveals a WBC count of 0.6 x 10^9/L with an ANC of 0.33 x 10^9/L.

LS denies cough, dyspnea, mucositis, dysuria, or diarrhea. Her blood pressure is 95/65 mm Hg and heart rate is 120 beats per minute.

Should LM be admitted to the hospital for her FN?
What empiric antibiotic treatment should LS receive?

A. Ampicillin/sulbactam + gentamicin
B. Cefepime
C. Meropenem + voriconazole
D. Piperacillin + tobramycin + vancomycin
Should LS receive a CSF at this point?

A. Yes, either filgrastim or pegfilgrastim
B. Yes, only filgrastim
C. No
Summary

- FN is an oncologic emergency that is associated with substantial morbidity, mortality, and cost.
- A proactive risk assessment is needed to identify patients at high risk of developing FN.
- Prophylactic use of CSF can reduce the risk, severity, and duration of FN.
- FN requires prompt assessment and empiric antibiotic therapy.
- Pharmacists can play a key role in the prevention and management of FN.
Questions?