Hematologic Derangements in Cancer Therapy

NEUTROPENIA

Defined as ANC (absolute neutrophil count < 500 cells/mm^3 or < 1000 cells/mm^3 with a predicted decrease to less than 500.
ANC = (% neutrophils + % bands from manual differential) x WBC
With severe neutropenia (< 500 cells/mm^3), infection with opportunistic infection, especially endogenous organisms
Fever is defined as a single oral temperature ≥ 38.3°C (101.0 °F) or a T ≥ 38.0°C (100.4 °F) for ≥ 1 hours.
Neutropenic Precautions

- Wash hands; change gloves between patients
- Private room
- Avoid personnel sick with viral or contagious illness
- No plants, stagnant water, fresh flowers, humidifiers or vaporizers
- Clean and disinfect equipment before patient contact
- Use separate stethoscope for each patient

G-CSF is commonly used to reduce the length and severity of neutropenia. The use of G-CSF is associated with fewer infections, a decreased incidence of febrile neutropenia, a decreased incidence of mucositis in selected populations, and a decreased number of days in the hospital.

A meta-analysis from SUNY Albany, 2002, found recombinant G-CSF (filgrastim and lenograstim) were associated with a reduced risk of febrile neutropenia (OR 0.38; 95% CI 0.29-0.49), and documented infection (OR 0.51, 95% CI 0.36-0.73) but a greater risk of bone pain (OR .9; 95% CI 1.6-4.8). There was a trend to decreased infection related mortality with the use of recombinant G-CSF (OR 0.60; 95% CI 0.30-1.22).

Recommendations of the American Society of Clinical Oncology for the use of Colony Stimulating Factors (CSF)

- Primary administration of CSF is nit recommended unless neutropenia prior to therapy, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow
- Current evidence supports that CSF should not be routinely used for patients with neutropenia but are afebrile.
- CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. The use of CSF in high risk patients may be beneficial (ANC < 100, uncontrolled primary disease, pneumonia, hypotension, MODS {sepsis}, and invasive fungal infection).
- CSF are recommended to help mobilize peripheral blood progenitor cells and after peripheral blood progenitor cell infusion.
- CSF should be avoided in patients receiving concomitant CTX and XRT. In the absence of CTX, in patients receiving large fields of radiotherapy, therapeutic use of CSF may be considered if prolonged delays due to neutropenia are expected.
- For adults, the recommended dose for G-CSF (filgrastim) are 5 mg/kg/d; GM-CSF (sargramostim) 250 mg/m^2/d.
- Start CSF 24-72 hours after CTX and continue until AND > 10,000.

Use of Antimicrobial agents in Neutropenic patients with Cancer

Evaluation
Without leukocytes, many common signs of infection will be absent.
Specimens should be sent immediately for culture of bacteria and fungi. If a central venous catheter is in place, draw ≥ 1 set of blood cultures from each lumen as well as from a peripheral vein. Send UCx if s/sx of UTI exist, if there is an indwelling Foley, or UA findings are abnormal. CSF specimens are not routinely collected but should be considered if CNS infection is suspected. CXR should be obtained if there are respiratory s/sx.

Determine if patient is at low risk for complications; determine if vancomycin therapy is necessary
Initial Therapy

- Monotherapy when vancomycin is not indicated and patient is low risk
  - Use cipro + Augmenting
- Two drugs without vancomycin
  - Choose aminoglycoside + antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem
- Vanocmycin + 1 or 2 antibiotics
  - Choose cefepime or ceftazidime plus vanco, with or without aminoglycoside; carbapenum + vanco, with or without aminoglycoside; or antipseudomonal penicillin + aminoglycoside and vancomycin.
- Vascular access devices may be left in place during initial treatment for most patients, even if infection of a local entry site or catheter related bacteremia is detected. *S aureus* and coagulase negative *Staph* usually respond to parenteral antibiotics without removal of the catheter. Catheter removal may be required for recurrent infection, no response after 2-3 days, evidence of tunnel or periport infection, septic emboli, hypotension with catheter use, or nonpatent catheter. Bacteremia due to Bacillus spp., P. aeruginosa, Stenotrophomonas maltophilia, C. jeikeium, or VRE, and fungemia due to Candida spp., often respond poorly to Abx, and prompt removal is recommended.

Modification of therapy in the first week

- Patient becomes afebrile in 3-5 days – directed antimicrobial therapy

- Persistent fever throughout the first 3-5 days – if no clinical worsening, continue same antibiotics; stop vanco if cultures do not yield organisms. If there is progressive disease, change Abx. If the patient is febrile after day 5, consider adding antifungal, with or without a change in the antibiotic regimen.

Duration of therapy

- Patient afebrile by day 3
  - If ANC ≥ 500 for 2 consecutive days, if there is no definite site of infection, and if culture results do not yield positive results, stop Abx once AF > 48°.
- Persistent fever day 3
  - If ANC ≥ 500, stop Abx therapy 48 hours 4-5d after AND ≥ 500
- Antiviral drugs are not recommended unless clinical or laboratory evidence of viral infection is present.
- Use of CSF is not routinely used but should be considered in certain cases with predicted worsening of course.
- Use of Abx prophylaxis is not routine. EXCEPTIONS: TMP-SMX to prevent PCP pneumonitis; fluconazole and antivirals (acyclovir or ganciclovir) for patients undergoing allogenic hematopoietic stem cell transplantation.

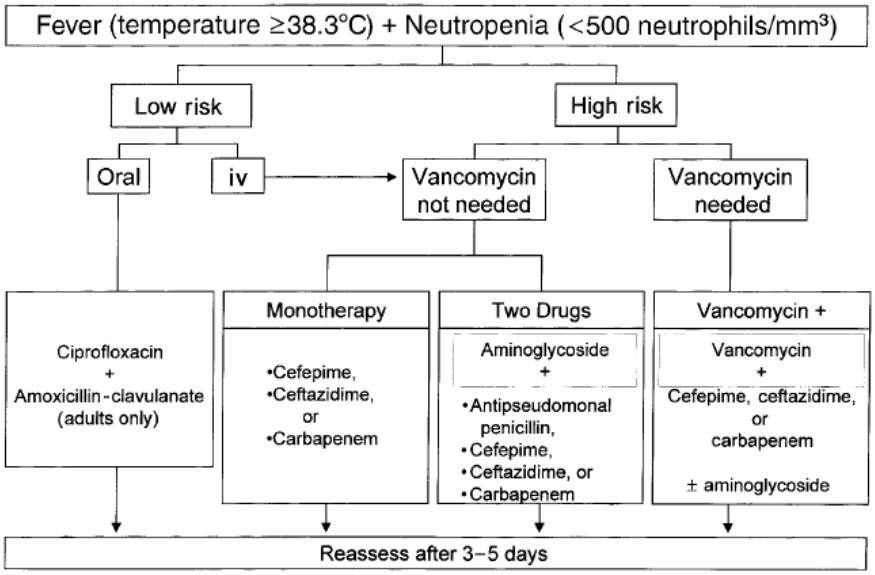

Figure 1. Algorithm for initial management of febrile neutropenic patients. See tables 3 and 4 for rating system for patients at low risk. Carbapenem, imipenem or meropenem.

Table 3. Factors that favor a low risk for severe infection among patients with neutropenia.

Absolute neutrophil count of ⩾100 cells/mm³
Absolute monocyte count of ⩾100 cells/mm³
Normal findings on a chest radiograph
Nearly normal results of hepatic and renal function tests
Duration of neutropenia of <7 days
Resolution of neutropenia expected in <10 days
No intravenous catheter–site infection
Early evidence of bone marrow recovery
Malignancy in remission
Peak temperature of <39.0°C
No neurological or mental changes
No appearance of illness
No abdominal pain
No comorbidity complications[a]

NOTE. Data are adapted from [4, 42–49, 51–53].

[a] Concomitant condition of significance (e.g., shock, hypoxia, pneumonia or other deep-organ infection, vomiting, or diarrhea).

Table 4. Scoring index for identification of low-risk febrile neutropenic patients at time of presentation with fever.

Characteristic	Score
Extent of illness[a]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age <60 years[b]	2

NOTE. Highest theoretical score is 26. A risk index score of ⩾21 indicates that the patient is likely to be at low risk for complications and morbidity. The scoring system is derived from [50].

[a] Choose 1 item only.

[b] Does not apply to patients ⩽16 years of age. Initial monocyte count of ⩾100 cells/mm³, no comorbidity, and normal chest radiograph findings indicate children at low risk for significant bacterial infections [46].

ANEMIA

Often complicates cancer management due to chronic disease, iron deficiency, or induced from chemotherapy or radiation. Erythropoietin has been used to treat chemotherapy induced anemia. Recent studies show that this may increase risk for hypercoagulability. However, a recent study showed improved oxygen delivery to tumor sites with the use of recombinant human erythropoietin independent of its effects upon hemoglobin.

In our institution, we tend to transfuse to maintain a Hemoglobin and Hematocrit of 8 and 25, respectively. In patients with cancer or with other medical comorbidities, higher levels of 10 gm and 30%, respectively, are sought for better wound healing and oxygen delivery.

THROMBOCYTOPENIA

Currently, we have no protocol utilizing recombinant human megakaryocyte growth and development factor. In fact, one case report describes the development of anti-thrombopoeitin antibodies

More often, an evaluation will be necessitated after a patient develops thrombocytopenia while on heparin for venous thrombosis. In this instance, it is necessary to send sera for anti-platelet antibodies (a.k.a. heparin induced antibodies). If HIT is documented, a six month course of treatment with Hirudin (lepirudin) will be indicated. Risk of anaphylaxis with lepirudin $\approx$ 0.015% on first exposure and 0.16% in reexposed patients, particularly when treated within 3 months of a previous exposure.

A moderate risk of bleeding exists once platelet counts < 50,000 cells/mm^3., and major risk is associated with platelet counts less than 20,000 cells/mm^3. Critical risk occurs with platelet counts < 10,000 cells/mm^3 because fatal CNS bleeding, GI hemorrhage, and respiratory tract hemorrhage are more likely to occur. It is our practice to preoperatively replace platelets for counts < 50,000 in anticipation of surgical bleeding. For platelet counts < 10,000 cells/mm^3, platelet transfusion is given due to the risk of spontaneous bleeding.

Sources

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