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CME CREDIT

Inpatient management of acute leukemia

KEY POINTS:

For patients with acute leukemia, there are four medical emergencies that require immediate attention: infection, hemorrhage, hyperleukocytosis, and tumor lysis syndrome.

If a febrile patient has an absolute neutrophil count less than 1.0×10^9/L, the physician should obtain blood, urine, and sputum cultures, order a chest radiograph, and start broad-spectrum antibiotics immediately to cover gram-negative organisms, even if a source of infection is not defined

During chemotherapy, bone marrow aplasia lasts from 4 to 5 weeks, during which the patient needs intensive support for anemia, thrombocytopenia, and leukopenia.

In general, patients receive red cell transfusions to keep the hemoglobin level higher than 9 g/dL.

ABSTRACT: Inpatients with acute leukemia need meticulous supportive care, which can be complex and challenging. The physician must be vigilant for infection, hemorrhage, and other complications. Aggressive transfusion support is often necessary, but can itself cause complications.

Although acute leukemia is curable, its treatment is toxic, and meticulous medical management is needed for optimum results. Many reviews of acute leukemia discuss the relative merits of various chemotherapeutic strategies,[1–4] but few cover the day-to-day management of patients receiving myelosuppressive chemotherapy.

This review examines the supportive care of patients hospitalized for acute leukemia, as a guide for clinicians faced with their management. Readers seeking more detailed information can consult recent reviews of acute leukemia's clinical presentation.[5,6]

MANAGING ACUTE LEUKEMIA AT PRESENTATION

Most patients with acute leukemia need hospitalization at the outset because of the multiple complications of both the disease and its treatment. There are four medical emergencies that require immediate attention: infection, hemorrhage, hyperleukocytosis, and tumor lysis syndrome.

Infection

Although acute leukemia can present with tumor fever, the most common cause of fever in patients with acute leukemia is infection. If a patient with fever is neutropenic (as most are, with an absolute neutrophil count less than 1.0×10^9/L), the physician should:

- Obtain blood, urine, and sputum cultures.
- Order a chest radiograph.
- Start broad-spectrum antibiotics immediately to cover gram-

negative organisms, even if a source of infection is not defined.[7,8]

The choice of antibiotic is controversial; some studies indicated that ceftazidime or imipenem by themselves are as effective as the usual combination of an extended-spectrum penicillin with an aminoglycoside.[9–12]

Broad-spectrum antibiotics should also be started empirically if a patient develops a fever while undergoing chemotherapy. Because most patients with leukemia have indwelling central venous catheters, which increase their risk for gram-positive bacteremia, vancomycin can be added to the initial antibiotic regimen to treat this possibility.[13,14]

Hemorrhage

Acute leukemia causes bone marrow failure, which usually leads to severe thrombocytopenia, increasing the risk of bleeding. Most patients present with bruising, minor mucosal bleeding, or petechiae, but some present with active hemorrhage. Hemorrhage is more likely in patients with fever, infection, and coagulopathy and should be aggressively treated with platelet transfusions.

Leukostasis is a medical emergency, as it increases the risk of intracranial hemorrhage

Disseminated intravascular coagulopathy is most common in acute promyelocytic leukemia, although it occasionally can be a presenting feature or complication of acute leukemia of any type,[15–17] and often either manifests or worsens after cytotoxic chemotherapy is started. Disseminated intravascular coagulopathy generally presents as bleeding in excess of what the platelet count would predict. Laboratory studies usually show:

- Low fibrinogen levels.
- Prolonged prothrombin and activated partial thromboplastin times.
- Elevated D-dimer levels.
- *Normal* antithrombin III levels—unlike in the coagulopathy of septic shock or obstetric emergencies.[18] A component of fibrinolysis may also be present.[19]

When a diagnosis of disseminated intravascular coagulopathy is suspected, the physician should confirm and aggressively treat it with:

- Cryoprecipitate, to raise fibrinogen levels to more than 150 mg/dL.
- Fresh-frozen plasma, to shorten prothrombin and activated partial thromboplastin times to normal.
- Platelet transfusions, to raise the platelet count to more than 50×10^9/L.
- All of the above, if there is evidence of active bleeding.

The role of heparin in low doses to treat disseminated intravascular coagulopathy is controversial, as are antifibrinolytics.[20]

Disseminated intravascular coagulopathy usually abates in about 1 week but can cause death early on from either intracranial or pulmonary hemorrhage. Suspected pulmonary hemorrhage should be treated with steroids in high doses.[21]

Hyperleukocytosis

When the blast count increases to 100×10^9/L, the disruption of blood flow characteristic of acute leukostasis may occur. Common symptoms include headache, focal neurologic deficits, and visual disturbances. Leukostasis constitutes a medical emergency, as it increases the risk of an intracranial hemorrhage.[22] To prevent leukostasis, if the blast count approaches this level the physician should:

- Give hydroxyurea or cytarabine immediately.
- Perform leukopheresis as needed to control the blast count.
- Start definitive cytotoxic chemotherapy as soon as the diagnosis is secure.[23]

The role of cranial radiation therapy to reduce the incidence of intracranial hemorrhage is controversial.[22]

Tumor lysis syndrome

Many patients with acute leukemia have signs and symptoms of rapid cell turnover at diagnosis. However, tumor lysis syndrome, caused by rapid destruction of leukemic blasts, usually occurs only after chemotherapy is started. The characteristic features of this syndrome are renal failure, hyperuricemia, hyper-

kalemia, hyperphosphatemia, and hypocalcemia.[24] Tumor lysis syndrome is almost universal in patients with B-cell acute lymphocytic leukemia and should be anticipated.

Tumor lysis syndrome can usually be prevented by administering adequate hydration during chemotherapy and by giving allopurinol prophylactically, but occasionally the urine requires alkalinization to make uric acid more soluble.[25] Dialysis is rarely necessary but is effective if more conservative measures fail.

Precautionary measures

Patients with newly diagnosed acute leukemia also require other, less urgent interventions. Indwelling central venous catheters are usually placed early after diagnosis to provide adequate long-term intravenous access. An assessment of myocardial function, such as a multiple gate acquisition analysis (MUGA) scan or echocardiogram, is usually performed before potentially cardiotoxic chemotherapy begins (ie, with daunorubicin).

MANAGING ACUTE LEUKEMIA DURING CHEMOTHERAPY

The goal of induction therapy is to achieve complete remission. This is usually accomplished with chemotherapy designed to rapidly induce bone marrow aplasia. Aplasia lasts from 4 to 5 weeks, during which the patient needs intensive support for anemia, thrombocytopenia, and leukopenia.

Anemia

In general, patients with acute leukemia receive red cell transfusions to keep the hemoglobin level higher than 9 g/dL. There is no advantage in allowing lower hemoglobin levels, and there is no need for higher hemoglobin levels if there is no cardiopulmonary compromise.

Red cell transfusions can cause both immune and nonimmune reactions, but premedications are not routinely given unless such complications have been documented to occur previously.[26] Transfused red cells should be leukocyte-poor to reduce the risk of alloimmunization and nonhemolytic febrile transfusion reactions.[27] Patients who may need a bone marrow transplant should receive irradiated red cells to prevent transfusion-associated graft-versus-host disease, which is rare but lethal.[28]

Candidates for bone marrow transplantation should also receive only blood products that are seronegative for antibodies to cytomegalovirus (CMV), to prevent seroconversion.[29] If the patient subsequently proves to be CMV-seropositive, then CMV-seropositive products are acceptable. Recent studies have indicated that leukocyte-filtered blood products are a suitable substitute for CMV-seronegative products if necessary.[30]

Thrombocytopenia

Platelet transfusions must be readily available to treat acute leukemia successfully. The risk of hemorrhage increases as the platelet count falls below 20×10^9/L.[31] In general, random-donor platelets are transfused to keep the platelet count above this threshold. However, in patients without fever, disseminated intravascular coagulopathy, or infection, platelet transfusions can be withheld until the count approaches 5×10^9/L.[32]

Patients who have reactions to platelet transfusions often receive premedications before subsequent transfusions, although the efficacy of premedication is uncertain,[33] and the optimal premedication schedule is unknown.[34] The most common reactions are fever (which usually responds to acetaminophen), hives or itching or both (which often respond to diphenhydramine), and rigors (which may respond to meperidine).

A minority of patients become alloimmunized to platelet transfusions from random donors and require either single-donor units or HLA-matched units.[35] These patients are at higher risk of bleeding owing to their inability to maintain an adequate platelet count. For patients with refractory thrombocytopenia and bleeding, antifibrinolytic agents such as epsilon aminocaproic acid may be given to reduce bleeding complications.[36]

Bone-marrow transplant candidates should receive only CMV-negative blood products

Leukopenia

Infection is the primary complication of leukopenia. Since nearly all patients treated for acute leukemia are severely leukopenic for several weeks, nearly all acquire an infection, usually bacterial. The initial management of fever in the neutropenic host is discussed above.

Prophylactic antibiotic treatment is controversial. Several studies have clearly demonstrated a reduction in the incidence of documented gram-negative bacterial infections in patients treated prophylactically with fluoroquinolone antibiotics.[37–39] However, these studies have not consistently demon-

strated a reduction in the use of antibiotics or length of hospitalization. More important, none have demonstrated a reduction in mortality or increase in survival.[40]

Further, prophylactic use of antibiotics increases the incidence of gram-positive infections[41] and may promote the emergence of antibiotic-resistant strains of bacteria.[42,43]

Prophylactic antiviral and antifungal treatment is recommended. Although effects on survival are difficult to demonstrate, randomized studies have demonstrated a reduction in the incidence of acute herpes simplex infections with prophylactic acyclovir treatment,[44] and in the incidence of fungal infections with prophylactic treatment with either fluconazole[45] or low-dose amphotericin B.[46]

Treat resistant fever empirically with amphotericin B

Recurrent or persistent fever despite treatment with broad-spectrum antibiotics may indicate a fungal infection and should be treated empirically with amphotericin B.[8,47] Fluconazole does not cover *Aspergillus* species and is not recommended as empiric therapy.[48]

Amphotericin B can cause severe side effects, which may be lessened by adding hydrocortisone to the intravenous preparation and by giving acetaminophen and diphenhydramine as premedication. Amphotericin B also causes wasting of potassium and magnesium from the distal renal tubule; the former can be mitigated by adding amiloride by mouth.[49]

Liposomal preparations of amphotericin B may be useful in patients who cannot tolerate the renal side effects of standard preparations.[50]

AFTER CHEMOTHERAPY

After chemotherapy, as the leukopenia and fever resolve and the absolute neutrophil count rises above 0.5×10^9/L, antibiotics can be discontinued if there is no bacteremia. However, patients must be carefully observed for recurrent fever, which may indicate an inadequately treated infection. In this situation, pain in the right upper quadrant of the abdomen and elevated levels of alkaline phosphatase suggest hepatosplenic candidiasis and should be evaluated by computed tomography.[51]

Elderly patients are more likely than younger patients to incur infectious complications and morbidity from prolonged leukopenia.[3] Several large studies consistently demonstrated that hematopoietic growth factors accelerate the recovery of neutrophils after chemotherapy for acute leukemia in the elderly and do not accelerate leukemic regrowth.[52–56] However, the results were inconsistent regarding any reduction in infectious morbidity and mortality, with no clear evidence of a survival benefit. Therefore, routine use of hematopoietic growth factors cannot be recommended.

Patients are discharged when they are afebrile and ambulatory with adequate neutrophil counts. Patients with identified sources of infection often require prolonged courses of intravenous antibiotics, which can be given safely at home. ■

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