The Adult Leukemias - Part 1: Acute Myeloid Leukemia

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Abstract

Acute Myeloid or Myelogenous Leukemia (AML) is a rare malignancy characterized by bone marrow infiltration of abnormal hematopoietic precursors and resulting disruption of normal production of red blood cells, white blood cells, or platelets. The FAB (French-American-British) classification subdivides AML into separate groups depending on abnormal cell morphology. Secondary AML may occur after treatment with alkylating agents and usually has a poorer prognosis than de novo leukemia. Overall prognosis remains guarded, with cure rates ranging from 0-60% depending on patient characteristics, leukemia cell type, and cytogenetic abnormalities. AML is sometimes discovered on a routine blood test in an asymptomatic individual; more often patients have constitutional complaints arising from anemia, leukocytosis or neutropenia, or thrombocytopenia. Blasts may be present in the peripheral blood, and are >30% in the bone marrow. In AML, >3% of these blasts are myeloperoxidase positive on staining. The presence of chromosomal translocations such as t(15;17) and t(8;21) is a good prognostic indicator; having normal chromosomes is intermediate in prognosis, and any chromosomal deletion or addition (-5, -7, trisomy 8) is a poor prognostic indicator. Treatment is tailored to the specific abnormality and FAB subtype, with particular subtypes having more favorable outcomes. Subcategorizing leukemias into different groups based on morphology, cytogenetics, and predicted outcome may lead to more specific and effective chemotherapeutic regimens and hopefully more cures in AML patients.

INTRODUCTION TO AML

Acute myeloid leukemia (AML) is a rare malignancy that is characterized by infiltration of bone marrow by abnormal hematopoietic progenitors that disrupts normal production of erythroid, myeloid, and/or megakaryocytic cell lines. It can be subdivided by the FAB (French-American-British) system into specific types depending on which cell lines are involved. AML subtypes (M0-M7) are determined by cell morphology with particular subtypes such as M3 (acute promyelocytic leukemia or APL) having a more favorable outcome. By classifying AML in this manner, developed treatments can more specifically eradicate the particular defective cell clone and hopefully provide a better outcome after therapy. More relevant than subtype, however, is the leukemia cell karyotype (cytogenetics). See table1.

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Overall incidence of AML is approximately 4 in 100,000 in the United States and England,6 and increases with age from 1 in 100,000 in people younger than 35 years to 15 in 100,000 in those older than 75 years.4 Rates are slightly higher in males and in whites. Although in general the etiology is unknown, AML is the leukemia most strongly linked to radiation, chemical exposure (benzene), or prior use of alkylating agents.1 There is a 20 fold increase of AML in Japanese atomic bomb survivors.5 The incidence of AML is 10 times higher in manufacturing workers exposed to benzene.6 Children who have received epipodophyllotoxins for ALL are at an increased risk of AML in later years.4 Secondary AML may occur 1-7 years after treatment with alkylating agents or other chemotherapy drugs and has a poorer prognosis than de novo leukemia if, as is usually the case, cytogenetics are abnormal. In addition, patients with myelodysplastic syndrome (MDS) may develop AML; 25% of AML patients have a history of MDS.7 Several congenital disorders terminate in AML - Down’s syndrome (20 times the risk), Fanconi’s anemia, Klinefelter’s syndrome, Turner’s syndrome, and Wiskott-Aldrich syndrome.4 The overall prognosis for AML remains guarded, with the cure rate with conventional therapies ranging from 0-60% depending on patient and leukemia cell characteristics including age, karyotype, the presence of an antecedent hematological disorder, performance status, and organ function.

PRESENTATION

Occasionally AML is discovered on a routine blood test in asymptomatic patients, but most patients have constitutional complaints arising from disruption of normal blood component production. These include fatigue and shortness of breath (anemia), bleeding and bruising (thrombocytopenia), and fever with or without infection (neutropenia). The most common infections are upper respiratory infections, though the occasional patient will present with pneumonia. Bone pain, infiltration of skin (leukemia cutis), gingiva, or other soft tissues usually suggests monocytic variants such as FAB M4 or M5.4 Less often, patients may have collections of myeloblasts/chloromas or granulocytic sarcomas in any soft tissue. These may be isolated findings initially, however, bone marrow infiltration is inevitable and treatment is therefore warranted.

Laboratory studies usually reveal pancytopenia, although any combination of anemia, thrombocytopenia, and leukopenia or leukocytosis may exist. Blasts and other immature white blood cells may be present in the peripheral blood, and because of rapid cell turnover, lactate dehydrogenase and uric acid may be elevated. In acute promyelocytic leukemia (APL) coagulation profiles should be evaluated carefully as disseminated intravascular coagulation (DIC) may occur when these cells lyse and release procoagulants. Leukocytosis may also be present and is a medical emergency, as leukostasis in perivascular tissues can cause headaches, altered mental status, dyspnea, and ultimately fatal pulmonary or intracranial hemorrhages.

DIAGNOSIS

Acute leukemias can usually be diagnosed from the peripheral smear, but bone marrow aspirate and biopsy should always be performed to determine proper classification. The bone marrow aspirate has more than 30% blasts (< 5% blasts is normal) of which >3% are positive for myeloperoxidase (MPO) stain. Special stains help determine specific FAB subtype. Patients with M4 or M5 morphology are positive for monocytic stains (peroxidase and esterase). Patients with M6 disease have diffuse cytoplasmic positivity for PAS (periodic acid Schiff) stain. Histochemical stains on bone marrow blasts are crucial for diagnosis, but cell immunophenotype and electron microscopy are helpful in difficult cases. Patients negative by all stains (AUL, acute undifferentiated leukemia) are usually treated as AML if immunophenotyping demonstrates myeloid markers.

Immunophenotype of AML blood or marrow should show myeloid markers such as CD13, CD14, CD15, and CD33.4 Auer rods are cytoplasmic inclusion bodies found in myeloblasts and monoblasts and, if present, are indicative of AML. Additional studies (e.g. CD41, electron microscopy) may help in diagnosing subtype M7. In acute promyelocytic leukemia, M3 subtype, the bone marrow may have less than 30% blasts but usually more than 70% progranulocytes.
Cytogenetics are preferably done on bone marrow, and are abnormal in 70% of patients.6

TREATMENT

Although AML was essentially a universally fatal disease 30 years ago, improvements have been made since then, with 15% of patients now being cured with current therapy regimens and improved supportive care. Initial treatment for AML is aimed at eradicating the leukemic clone and allowing reestablishment of normal hematopoiesis. There are usually 2 components of therapy - induction into remission and post remission therapy. Most AML subsets are treated similarly with the combination of cytarabine (Ara-C) given by continuous infusion for 7 days and by 3 days of bolus anthracyclines (Daunorubicin, Adriamycin, Idarubicin). This is the 7+7 regimen which produces a 70% complete remission rate.6 Complete remission (CR) is defined as circulating neutrophils > 1,500/ul, platelets >100,000/ul, bone marrow blasts <5% with >20% cellularity and normal maturation in all cell lines.8 High dose ara-C has improved prognosis overall, but particularly among younger patients and those with favorable karyotypes. Idarubicin appears to be superior to other anthracyclines. In APL, or the M3 subtype, the use of ATRA (all trans-retinoic acid), an oral differentiating agent, with chemotheraapy as indicated (e.g. Idarubicin) frequently (70%) results in prolonged remissions and probable cure. Allogeneic bone marrow transplant in first remission is reserved for patients with a poor prognosis with chemotherapy and is offered to all patients who relapse on frontline induction chemotherapies. Other combinations of chemotherapeutic agents are currently being investigated, however the overall prognosis for patients with AML, especially those with cytogenetic abnormalities other than t(15;17), t(8;21), and inversion 16 remains poor. See table 2. For this reason such patients should receive investigational therapies including bone marrow transplant if a matched donor is available.

Figure 2

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>FAB</th>
<th>Overall Incidence (%)</th>
<th>Complete Remission Rate (%)</th>
<th>Cure Rate</th>
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<tbody>
<tr>
<td>t(8;21)</td>
<td>M2</td>
<td>50</td>
<td>90</td>
<td>75</td>
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<td>M4</td>
<td>5-10</td>
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<td>40</td>
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<tr>
<td>t(16;16)</td>
<td>M3</td>
<td>10</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>-5, -7, t(16)</td>
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<td>20-30</td>
<td>50-60</td>
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<tr>
<td>1q22</td>
<td></td>
<td>10-20</td>
<td>10-15</td>
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CONCLUSION

Significant progress has been made in the treatment and potential for cure in patients with AML. Advances in supportive care have greatly improved the quality of life of patients receiving chemotherapy for leukemia. Continued research is necessary to develop new therapies specific to the defective clonal element responsible for leukemias and further improve clinical outcome in these patients.

References

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