6th lecture in hematology by Dr.Alaa Fadhil Alwan

The Acute Leukemias

The acute leukemias are characterized by uncontrolled proliferation of hematopoietic precursor cells, with loss of maturation and differentiation. The malignant cells take over the bone marrow and suppress normal hematopoiesis. Before the development of effective chemotherapy, survival of patients with acute leukemia was usually only a few weeks or months.
The acute leukemias can be divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The only morphologic feature that unequivocally indicates lineage is the presence of linear reddish or maroon structures known as Auer rods, which are diagnostic of myeloid lineage.
The acute leukemias have been traditionally classified by the FAB (French-American-British) classification system. The FAB classification is based largely on morphology and a few cytochemical stains and has limited significance in terms of prediction of prognosis and choice of therapy. Another classification system published by the World Health Organization (WHO) which depends on cytogenetic and molecular studies .

COMPLICATIONS OF ACUTE LEUKEMIA

1• Suppression of normal hematopoiesis: Normal hematopoiesis is almost invariably suppressed. Consequences include increased risk of infection due to leucopenia and hemorrhage due to thrombocytopenia.
2• Metabolic complications: The high cell turnover of the malignant cells may result in hyperuricemia, hyperphosphatemia, and hyperkalemia which called tumor lysis syndrome and may lead to acute renal failure .
3• Hyperleukocytosis and leukostasis syndrome: A very high blast count, particularly myeloblasts, may increase the blood viscosity. Patients may develop a leukostasis syndrome characterized by altered mental status, respiratory failure, and congestive heart failure. Leukostasis can occur with blast counts 50,000, and the risk increases significantly with blast counts 100,000. Leukostasis is most common with AML, particularly cases with monocytic differentiation, but can also be seen with ALL, chronic myelogenous leukemia (CML), and, rarely, chronic lymphocytic leukemia (CLL).Hyperleukocytosis with leukostasis is a medical emergency; the blast count must be lowered as soon as possible.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Definition and Classification

Acute lymphoblastic leukemia represents a clonal proliferation of immature lymphocyte precursors.The cells may be B-cell precursors (~80 to 85% of cases) or T-cell precursors (~15 to 20% of cases). In rare cases, the lineage is unclear. The FAB classification divides ALL into three groups (L1, L2, and L3) based strictly on morphology. The L3 type consists of mature B cells (not precursors) and corresponds to blood involvement by Burkitt's lymphoma.

Epidemiology

ALL is the most common malignancy in childhood and represents ~85% of childhood acute leukemias. ALL also occurs in adults but is uncommon (~15% of adult acute leukemias). The highest incidence of ALL is between 1 and 5 years of age. There is a slight male predominance. There is a marked increase in risk of ALL in children with trisomy 21 (Down syndrome) and following exposure to ionizing radiation. However, in the majority of cases, there is no known predisposing factor.

FAB Classification of ALL

L1: Most common type in childhood. Monomorphic, small to intermediate-sized blasts that have round nuclei, scant cytoplasm, and inconspicuous nucleoli.
L2: Most common type in adults. Larger, more variable cells.
L3: Rare (~1–3% of ALL). The cells are characterized by deeply basophilic (blue) cytoplasm with prominent clear cytoplasmic vacuoles .

WHO Classification of ALL

Precursor B-cell ALL:
Cytogenetic subgroups (with oncogenes involved):
t(9;22)(q34;q11); BCR/ABL (the Philadelphia chromosome)
t(v;11q23); MLL rearranged (MLL = myeloid-lymphoid leukemia gene)
t(1;19)(q23;p13); E2A/PBX1
t(12;21)(p12;q22); TEL/AML1
Precursor T-cell ALL

Clinical Features

• Pallor and fatigue • Petechiae or other bleeding signs • Fever • Bone or joint pain: Bone or joint pain is common, probably due to expansion of the medullary cavity by the malignant cells. • Hepatosplenomegaly and lymphadenopathy
• CNS involvement: ALL can involve the central nervous system, testes in males may also be a site of relapse. Testicular involvement presents as painless enlargement of the testes.

Laboratory Investigation

Anemia and thrombocytopenia are almost present. The white cell count is variable: it may be high, normal, or occasionally decreased. Blasts are usually present on blood smear but may be absent or hard to find in up to 5% of cases (aleukemic leukemia). Serum uric acid and lactic dehydrogenase may be increased

Bone Marrow

The bone marrow in ALL usually shows a monomorphic population of blasts, with marked decrease in normal hematopoietic precursors of all types . “Block” PAS reactivity may be present. Reactivity for myeloperoxidase, Sudan black B, and specific and nonspecific esterases are absent.

Immunophenotype

Immunophenotyping is usually performed by flow cytometry on either blood or a bone marrow aspirate.

Cytogenetics

Cytogenetic analysis has become critical for prediction of outcome and selection of therapy in ALL.

Molecular Diagnostic Tests

Molecular tests can also be used to detect chromosomal abnormalities not detected on standard cytogenetics.

Differential Diagnosis

1• Immune thrombocytopenic purpura (ITP): ITP presents with petechia or other signs of bleeding, mimicking a common presentation of acute leukemia. In ITP, the hemoglobin and white blood count are usually normal, and the patients otherwise appear healthy.
2• Aplastic anemia: Aplastic anemia presents with anemia, thrombocytopenia, and leukopenia and clinically may resemble aleukemic leukemia. Hepatosplenomegaly is usually absent. The diagnosis is based upon a hypocellular bone marrow without a predominance of blasts.
3• Chronic lymphocytic leukemia (CLL): CLL is characterized by a predominance of small mature-appearing lymphocytes instead of blasts. Flow cytometry of CLL demonstrates a mature B-cell phenotype rather than the immature phenotype seen in ALL. Chronic lymphocytic leukemia is characteristically a disease of adults, whereas ALL is more common in children.

4• Acute myeloid leukemia: AML, particularly minimally differentiated AML (M0 and M1 in the FAB classification), can be morphologically indistinguishable from ALL. Cytochemical stains and immunophenotyping usually permit distinction.

Treatment

Treatment of ALL is usually separated into three phases: remission induction, intensification (consolidation), and continuation (maintenance). Treatment includes several drugs that have different mechanisms of action. The total duration of therapy is 2 to 3 years. Treatment of the central nervous system (CNS) is an essential part of therapy, even in the absence of overt CNS involvement, to prevent CNS relapse.

1• Induction: Typical induction regimens include a corticosteroid (prednisone or dexamethasone), vincristine, and anthracycline. This phase lasts approximately 4 to 6 weeks and is designed to reduce the leukemic burden to clinically undetectable levels (ie, induce a complete remission [CR]).

2• Intensification (consolidation): Intensification regimens can include higher doses of the drugs used to induce remission or a combination of different drugs. Examples of consolidation regimens include (1) methotrexate with or without 6-mercaptopurine, (2) an epipodophyllotoxin such as VP16 with cytosine arabinoside (cytarabine; ara-C), or (3) a combination of vincristine, dexamethasone, L-asparaginase, doxorubicin, and thioguanine with or without cyclophosphamide. This phase typically involves repeated cycles of therapy over approximately 6 months (longer in high-risk patients).

3• Continuation (maintenance): This phase typically includes weekly methotrexate (orally or by intramuscular injection) and daily oral 6-mercaptopurine. This phase typically lasts approximately 2 to 21/2 years.

4• CNS therapy: Prophylactic CNS therapy is required in order to prevent CNS relapse. Intrathecal chemotherapy with methotrexate or cytosine arabinoside is used, together with high doses of drugs that cross the blood-brain barrier such as dexamethasone, methotrexate, or cytosine arabinoside. Craniospinal irradiation is used in patients with CNS involvement at diagnosis and in some patients considered at high risk for CNS relapse.

Prognosis

The prognosis of childhood ALL has improved dramatically. Over 95% of children achieve a complete response, and over 80% of children have longterm disease-free survival and are presumed cured. The prognosis in adults is less optimistic; less than 40% of adults are cured. Efforts have been made to stratify treatment based on prognosis: patients with favorable prognostic factors can be treated less aggressively, whereas patients with adverse prognostic factors may be treated more aggressively from the time of diagnosis. Nearly all adults with ALL are considered high risk. The initial risk stratification is based on age and WBC count, and then readjusted after cytogenetic results are available. Patients at particularly high risk (such as those with a Philadelphia chromosome) may be considered for allogeneic bone marrow transplant (BMT) in first CR.

Prognostic Factors in ALL

Factor	Favorable	Unfavorable
Age	2 to 10 years	Below 2 years or above 10 years
WBC count At diagnosis	Low WBC count	WBC >50,000
Phenotype	Precursor B cell	Precursor T cell Mature B cell
Chromosome abnormalities	Hyperdiploidy Trisomy 4 and trisomy 10	Pseudodiploidy t(2;8); t(8;22)] MLL alterations (11q23), t(9;22) (Philadelphia chromosome), t(1;19)
Sex	Female	Male
Ethnicity	Caucasian	African American, Hispanic

ACUTE MYELOID LEUKEMIA(AML)

Definition and Classification

There are 2 types of AML which may occur in adult: de novo AML and secondary AML.
• De novo (primary) AML occurs in patients with no previous history of hematologic disease. The patients tend to be younger, have a better response to therapy, and an overall better survival. Reciprocal chromosomal translocations are characteristically present.
• Secondary AML occurs in patients with a preceding hematologic disease such as a myelodysplastic syndrome or a chronic myeloproliferative disorder or in patients who have received chemotherapy for another malignancy. In general, secondary AML occurs in older patients and is associated with a poor response to therapy and an overall poor prognosis.
A critical distinction in AML is between acute promyelocytic leukemia (APL) and other subtypes because there is a unique therapy for APL called all-trans-retinoic acid (ATRA). All other subtypes are treated essentially the same.
The standard classification for AML has been the FAB classification which defines eight subtypes based on the degree of maturation and lineage differentiation. There are some clinical differences between the FAB subtypes; for example, the monocytic types (AML-M4 and AML-M5) associated with gums hypertrophy while Acute promyelocytic leukemia associated with disseminated intravascular coagulation (DIC).

FAB Classification of AML
M0 = AML with minimal evidence of myeloid differentiation
M1 = AML without differentiation
M2 = AML with differentiation
M3 and M3 variant = acute promyelocytic leukaemia
M4 = acute myelomonocytic leukaemia
M5 = acute monoblastic (M5a) or monocytic (M5b) leukaemia
M6 = acute leukaemia with at least 50% erythroblasts in the bone marrow
M7 = acute megakaryoblastic leukaemia

WHO Classification of AML
AML with recurrent cytogenetic translocations:
AML with t(8;21); AML1(CBF beta)/ETO. Favorable
APL AML with t(15;17) and variants; PML/RAR alfa). Favorable
AML with inv(16), or t(16;16) CBF beta/MYH11X). Favorable
AML with 11q23 (MLL) abnormalities. Unfavorable
AML with multilineage dysplasia: Generally unfavorable
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome
AML and myelodysplastic syndromes, therapy related
Epipodophyllotoxin related (some may be lymphoid)
Other types:
AML not otherwise categorized
AML minimally differentiated
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryocytic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis

Epidemiology

Acute myeloid leukemia occurs at all ages but is predominantly a disease of older adults. The incidence rises progressively with age. Approximately 85% of acute leukemias in adults are AML, compared to 15% of acute leukemias in children. Predisposing factors for AML include trisomy 21, Fanconi's anemia, Exposure to ionizing radiation and Benzene and its derivatives

Clinical Features

The clinical presentation of AML symptoms resembles that of ALL. Tissue involvement is more common in AML than in ALL. Skin involvement occurs in approximately 10% of patients, particularly in patients with monocytic subtypes (M5); it presents as violaceus nontender plaques or nodules. Involvement of the gums is common, and patients may present initially to the dentist, complaining of bleeding gums.

Metabolic complications of AML may include hyperuricemia, hyper- or hypokalemia, hyperphosphatemia, and the tumor lysis syndrome with acute renal failure. Disseminated intravascular coagulation may occur in AML. It is most frequent in acute promyelocytic leukemia (APL) but may also occur with other types.

Laboratory Investigation

Same as in ALL. The only morphologic feature that absolutely confirms myeloid lineage is the presence of Auer rods.

Bone Marrow

The bone marrow is typically hypercellular, with a predominance of blasts or other immature cells. Normal hematopoietic precursors are decreased.

Immunophenotype

Immunophenotyping by flow cytometry is most useful in identifying myeloid lineage and distinguishing between AML and ALL. Phenotyping can suggest specific subtypes of AML, particularly megakaryocytic leukemia, but definitive subclassification usually requires correlation with morphology and cytochemical stains.

Cytogenetics

Cytogenetic analysis has become critical in the diagnosis and treatment of AML.As in ALL,

Differential Diagnosis

Same as in ALL

Treatment

Treatment of AML divided into remission induction and post-induction (post-remission) phases.

1• Remission induction: Standard induction therapy includes an anthracycline and cytosine arabinoside .

2• Post induction (post remission) therapy: Post induction regimens can include chemotherapy at various levels of intensity (maintenance, consolidation, or intensification), allogeneic bone marrow transplant or high-dose chemotherapy with autologous bone marrow transplant. The choice of therapy depends on the individual patient, the prognosis as determined by cytogenetic results on the bone marrow among other factors, and also whether the patient has a suitable bone marrow donor.

Allogeneic bone marrow transplant: Allogeneic BMT performed during remission is the most effective therapy available for decreasing relapse of AML. It is used predominantly in younger patients considered to be at high risk of relapse. Older individuals are generally not considered candidates for allogeneic transplant due to higher transplant-related mortality, but the age limit has been rising because of improvements in supportive care.

Autologous bone marrow transplant: Hematopoietic progenitor cells can be harvested after the patient has achieved a CR and either given after intensive chemotherapy in first remission or saved to be used in case of relapse. The early morbidity and mortality of autologous BMT is lower than that of allogeneic BMT, but the relapse rate is higher, giving an overall survival

that is approximately equivalent. Autologous BMT can be used in patients who are too old for allogeneic BMT or who do not have a suitable donor.

Prognosis

The overall long-term disease-free survival of patients less than 65 years old with AML is approximately 40%. The prognosis is worse for older patients and those with secondary AML. Patients with AML can be divided into three broad prognostic groups, predominantly on the basis of cytogenetic results:

1• Favorable prognostic group: This group includes patients <60 years old with the t(8;21), t(15;17), inv(16), or t(16;16) cytogenetic abnormalities, no previous hematologic disease, and AML that is not therapy related. This group makes up ~20% of patients <60 years. They have a high CR rate (>85%) and a relatively low risk of relapse (30 to 40%).

2• Unfavorable prognostic group: This group includes patients with cytogenetic abnormalities involving more than two chromosomes, monosomies of chromosomes 5 or 7, deletion of the long arm of 5 (del5q), or abnormalities of the long arm of chromosome 3. Patients with abnormalities involving chromosome 11q23 (MLL gene) are sometimes also considered to be in this group. These abnormalities are more often present in older individuals and patients with secondary AML. This group makes up ~15% of patients who are 15 to 60 years old. They tend to have a lower CR rate and a higher relapse rate, and survival at 5 years is <20%. No current treatment approach is considered satisfactory for these patients. Patients over 60 years of age generally have an unfavorable prognosis, with 5-year-survival rates <10%.

3• Intermediate (standard) prognostic group: Patients in this group have either a normal karyotype or chromosomal abnormalities not included in the other groups.

Special Types of Acute Myeloid Leukemia

• Acute promyelocytic leukemia (APL; FAB-M3): Acute promyelocytic leukemia with the t(15;17) is distinct because it responds to a specific therapy: ATRA. Acute promyelocytic leukemia most commonly occurs in younger individuals. The white cell count is often relatively low, and DIC is very common. All-trans retinoic acid induces differentiation of the leukemic promyelocytes; it is not a cytotoxic agent and does not induce bone marrow aplasia. It is able to induce a complete hematologic remission in the majority of APL patients, a cytotoxic agent(doxorubicin) given, either together with ATRA to induce remission or as consolidation following remission induction with ATRA. All-trans-retinoic acid also improves the coagulopathy associated with APL. All-trans-retinoic acid may be associated with the “retinoic acid syndrome,” which includes a capillary leak syndrome with fever, respiratory failure, impaired renal function, and, in some patients, cardiac failure. Arsenic trioxide also appears to be effective in APL.