

Acute myelomonocytic leukemia

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Abstract

Acute myeloblastic leukemia (AML) is a group of malignant bone marrow neoplasms of myeloid precursors of white blood cells. Acute myelomonocytic leukemia (AML-M4) is a common type of pediatric AML. However, the condition is rare and represents approximately 3 % of all leukemias during childhood and has an incidence of 1.1 – 1.7 per million per year. The symptoms may be aspecific: asthenia, pallor, fever, dizziness and respiratory symptoms. More specific symptoms are bruises and/or (excessive) bleeding, coagulation disorders (DIC), neurological disorders and gingival hyperplasia. Diagnostic methods include blood analysis, bone marrow aspirate for cytochemical, immunological and cytogenetical analysis, and cerebrospinal fluid (CSF) investigations. A characteristic chromosomal abnormality observed in AML-M4 is inv(16). Treatment includes intensive multidrug chemotherapy and in selected cases allogeneic bone marrow transplantation. Nevertheless, outcome of AML remains poor with an overall survival of 35-60%. Children with AML-M4 carrying the inv(16) abnormality have a better prognosis (61% 5-year overall survival). New therapeutics are required to increase the probability of cure in this serious disorder.

Keywords

Acute non-lymphocytic leukemia (ANLL), Acute myeloblastic leukemia (AML), Acute myelomonocytic leukemia, AML-M4, AML-M4eo

Disease name and synonyms

- Acute myelomonocytic leukemia
- Acute myeloblastic leukemia (AML) M4 (FAB-classification)
- Acute myeloid leukemia with inv(16)(p13;q22) or t(16;16)(p13;q22) (WHO classification)
- Acute non-lymphocytic leukemia (ANLL)

Definition

AML-M4 is defined by more than 20% (WHO-classification) or more than 30% (French-American-British (FAB) classification) of myeloblasts in the bone marrow aspirate. Moreover, 20% of non-erythroid cells are of monocytic origin.

The M4eo variant is characterised by more than 5% of abnormal eosinophilic cells.

Differential diagnosis

Other malignancies that should be differentiated from AML are: [acute lymphocytic leukemia \(ALL\)](#), myelodysplastic syndrome (MDS), [chronic myeloid leukemia \(CML\)](#) including juvenile chronic myelomonocytic leukemia, bone marrow metastases of solid tumours such as [neuroblastoma](#), [rhabdomyosarcoma](#) and [Ewing sarcoma](#), bone marrow invasion by non-Hodgkin lymphoma (NHL).

Differential diagnosis also includes non-malignant disorders such as transient leukemoid reactions, transient myeloproliferative syndromes, juvenile chronic arthritis, infectious mononucleosis, viral induced bone marrow suppression, aplastic anemia, congenital or acquired neutropenia and autoimmune cytopenia.

Etiology

Some congenital and acquired disorders may predispose to AML.

The congenital predisposing factors are:

- [Down syndrome](#)
- Twin with leukemia
- [Fanconi's anemia](#)
- [Bloom syndrome](#)
- [Ataxia teleangiectasia](#)
- [Neurofibromatosis type I](#)
- [Li-Fraumeni syndrome](#)
- [Congenital neutropenia \(Kostmann syndrome\)](#)
- [Klinefelter's syndrome](#)

Acquired predisposing factors include:

- Prenatal exposure to tobacco, marijuana, alcohol
- Pesticides, herbicides, benzene, petroleum
- Aplastic anemia
- Myelodysplastic syndrome
- [Paroxysmal nocturnal hemoglobinuria](#)
- Radiation
- Chemotherapy (epipodophyllotoxins, alkylating agents, anthracyclins)

Clinical presentation

Children with AML in general may present with a broad variety of (atypical) symptoms, which may range from minor symptoms to life-threatening conditions. Most patients will present with fatigue and/or asthenia, which is often accompanied by (persistent) fever. Severe infections may occur due to the diminished neutrophil count and function. Easy bruising (petechiae and/or purpura) may occur as well as enhanced bleeding (epistaxis, oral or gingival bleeding,

rectal blood loss, menorrhagia, cerebral hemorrhage). These bleeding disorders result from thrombocytopenia that may be associated with Disseminated Intravascular Coagulopathy (DIC), which can lead to life-threatening situations. The complications due to bleeding contribute for 7-10% to the mortality that is observed during the first days/weeks after diagnosis (Creutzig, 1987). However, complications due to hemorrhage are more frequent in promyelocytic leukemia (AML-M3) and monoblastic leukemia (AML-M5). Pallor may be predominant, and results from the decreased hemoglobin level. Pallor may be accompanied by dizziness, headache, tinnitus, collapses, dyspnea and/or congestive heart failure. Gingival hyperplasia may be present, but is not typical of AML-M4.

Dyspnea and/or hypoxia may also result from leukostasis, which results in a decreased blood flow in some organs (lungs, CNS, liver, skin) due to a dramatically increased White Blood Cell count WBC (>100.000/ml) leading to hyperviscosity.

Neurological symptoms may occur: headache, nausea, vomiting, photophobia, cranial nerve palsies, papil edema and/or nuchal rigidity. These symptoms may result from leukostasis, but may also reveal meningeal invasion by myeloblasts or be the presenting symptoms of a "chloroma", which is a soft tissue mass consisting of myeloblasts. These chloromas often have an orbital or periorbital localisation, or may arise around the spinal cord, causing paraparesis or "cauda equina" syndrome. CNS leukemic infiltration occurs in 6-16% of AML (Bisschop 2001, Abbott 2003), especially in AML-M4.

Renal insufficiency occurs seldomly. It is caused by hyperuricuria and/or hyperphosphaturia, leading to obstructing tubular deposits and oliguria/anuria. The etiology of these metabolic disorders is called the "tumour lysis syndrome", where myeloblasts lyse spontaneously. This situation is an emergency since life-threatening hyperkalemia may be associated, requiring hemodialysis or peritoneal dialysis.

Diagnostic methods

Routine blood analysis shows in the majority of patients a normocytic, normochromic anemia, which may be as low as 3 gr/dl. Reticulocyte count is low. Erythrocyte sedimentation rate (ESR) is often increased. Thrombocyte count is mostly decreased (<100.000/ml). WBC count may be decreased, normal or (substantially) increased. WBC differential (the percentage of each of the five types of white blood cells) may show myeloblasts that may contain Auer rods, which are needle-shaped accumulations of myeloid granules. However, myeloblasts are not

always observed in the differential, and only promyelocytes and/or myelocytes may be seen. Neutrophil count is often decreased.

A prolonged prothrombin time (PT) and or activated partial thromboplastin time (APTT) may reveal DIC. Additional screening then may show decreased fibrinogen levels, increased fibrinogen degradation products (FDP) or D-dimers, and decreased anti thrombin III levels. Blood chemistry analysis should include plasma electrolytes, uric acid, lactate dehydrogenase (LDH), creatinin and Blood Urea Nitrogen (BUN). A bone marrow aspirate is mandatory. Morphologic analysis after May-Grünwald-Giemsa staining generally shows a mixture of myeloblasts, monoblasts and promonocytes. The M4eo and M4baso subtypes are characterized by an excess of abnormal eosinophilic or basophilic cells. Special stainings (myeloperoxidase, Sudan black B, chloroacetate esterase, α -naphthyl acetate esterase) may help to make the distinction between the various subtypes of AML and ALL. Immunophenotyping usually reveals positivity for MPO, CD13, CD14, CD15, CD33, CD34, CD64, CD65, CD117 and HLA-DR.

A specimen of the bone marrow aspirate is also used for cytogenetic analysis in order to detect any of the several chromosomal abnormalities observed in AML. The most widely observed chromosomal abnormality in AML-M4 is the inv(16) aberration, which is typical of the M4eo variant. Inv(16) is associated with a good prognosis (Grimwade, 1988).

Cerebrospinal (CSF) analysis is also mandatory in order to exclude CNS invasion, which is defined as > 5 cells/ml and the presence of myeloblasts.

Radiological investigations include chest X-ray, abdominal ultrasound and in case of neurological symptoms computed tomography (CT) or magnetic resonance imaging (MRI) of the brain using appropriate contrast. Echocardiography should assess left ventricular contractility prior to starting chemotherapy.

Epidemiology

The incidence of pediatric AML is 4.8 – 6.6 per million per year in children <15 years (Gurney, 1995). There is no male or female preponderance. However, there is ethnic variation in incidence, since there is a higher incidence of pediatric AML in Asians and Hispanics as compared to non-Hispanic Caucasians in the USA (Gurney, 1995). Black children have a lower incidence of AML than Caucasians in the USA (Parkin, 1988). There is a peak incidence during infancy (Stiller 1995, Kaatsch 1995), but AML may occur throughout childhood.

As previously mentioned, the incidence is higher in some genetic congenital disorders. In Down syndrome, the relative risk of developing AML is 20, and reaches 153 during the first four years of life (Hasle, 2000). Children with Down syndrome may develop all types of AML, although there is a preponderance of megakaryocytic leukemia (AML-M7), which is very rare in the normal pediatric population.

AML-M4 represents \pm 20% of all pediatric cases of AML, and is more frequent among young children (<2 years). However, the condition is rare and represents approximately 3 % of all leukemias during childhood and has an incidence of 1.1 – 1.7 per million per year.

Management including treatment

AML remains a disease that is difficult to treat. Treatment consists of aggressive multidrug chemotherapy regimens, which are associated with non-negligible mortality and morbidity. The main drugs used for the treatment of AML are cytarabine, anthracyclins (daunorubicin, idarubicin and mitoxantrone) and etoposide. These key-drugs are repeatedly administered using various schemes of dosing and may be associated to drugs such as 6-thioguanine, dexamethasone and amsacrin. In most chemotherapy protocols, 4-6 courses of multidrug chemotherapy are administered with an interval of 3-4 weeks. A high dose and time-intensity may positively influence the outcome of the treatment. Chemotherapy is also administered intrathecally in order to treat or prevent CNS-leukemia.

Each course results temporarily in severe bone marrow suppression, leading to prolonged anemia, leukocytopenia, neutropenia and thrombocytopenia. This is often accompanied by (opportunistic) bacterial or fungal infections, which may be life threatening. Moreover, the chemotherapy courses result in mucositis, which is due to a cytotoxic effect of the chemotherapy on the epithelium of the intestinal tract, requiring various supportive care measures. The repeated administration of anthracyclins may cause a decrease in cardiac contractility on the short (months) and long term (years).

Supportive measures during and after treatment comprise:

- Anti-emetic compounds (ondansetron, granisetron, domperidone, dexamethasone, metoclopramide, alizapride, chlorpromazine).
- Analgetics (paracetamol, tramadol, morphine).
- Prophylactic and/or therapeutic antibiotics and antifungal compounds.

- Transfusions of leucocyte-depleted erythrocyte concentrates and/or thrombocyte suspensions.
- Enteral nutritional supplements or parenteral nutrition.
- Hematopoietic stem cell growth factors (G-CSF).

Bone marrow transplantation

Some patients may benefit from allogeneic bone marrow transplantation (alloBMT). Whether a patient with AML will be treated with alloBMT depends on the type of AML, the associated cytogenetic abnormality, the response to chemotherapy and the availability of a donor. This treatment is applied when complete remission is obtained after 2-4 courses of induction and consolidation chemotherapy, and aims at removing the minimal residual disease. The treatment consists of combining high-dose chemotherapy with Total Body Irradiation (TBI), which is followed by the reinfusion of HLA-identical hematopoietic stem cells of a sibling or a matched unrelated donor (MUD). The anti-tumour effect is obtained by the cytotoxic effects of the chemotherapy and radiotherapy and by immunological effects ("Graft-versus-leukemia" effect) caused by minor immunological disparities between donor and recipient. Although alloBMT has improved the outcome of AML patients, it remains a highly specialized treatment with high treatment-related mortality (10-15%) and morbidity (Stevens, 1998). Patients with AML-M4 carrying the inv(16) are generally not treated by alloBMT, since their disease is often curable by standard AML chemotherapy regimens.

Autologous stem cell transplantations have been performed in the past, but are generally not recommended anymore, since they do not seem to improve the outcome as compared to the current chemotherapeutic regimens (Ravindranath, 1996).

Radiotherapy

The main indication for radiotherapy (RT) is the previously mentioned TBI. Moreover, craniospinal irradiation may be indicated when CNS is invaded by myeloblasts, although repeated intrathecal chemotherapy has replaced RT in some protocols. Finally, RT is applied for the emergency treatment of chloroma in case of dural compression.

Outcome

As mentioned before, AML remains a difficult disease to treat. Some but small progress has been made during the last 2-3 decades. Less than 20% of the patients with a recurrence can be cured in the long term. Five year overall

survival generally does not exceed 60% (38-72%) (Michel, 1996). When a bone marrow donor is not available (which is the case in more than 50% of cases), the overall survival drops to 35-60% (Ravindranath, 1996; Perel, 2002). Several prognostic factors have been identified: age, WBC count, response to induction therapy, FAB-type of AML, leukemic cytogenetic abnormalities, Down syndrome.

The inv(16) chromosomal aberration is associated with a better prognosis as compared to the absence of cytogenetic abnormalities: 5-year overall survival of patients with inv(16) is 61% (Grimwade, 1998).

Novel therapies are emerging: new nucleoside analogues (fludarabine, cladribine, cyclopentenyl cytosine, clofarabine), monoclonal antibodies targeting CD33 and labelled with a radionuclide or toxic compound. Moreover, "targeted therapies" such as imatinib mesylate (Glivec®), fli-3 inhibitors and farnesyl transferase inhibitors, may act on tumour-specific cellular pathways, resulting possibly in less toxicity than the conventional chemotherapeutic compounds with hopefully better anti-tumour effect.

Unresolved questions and conclusion

The mechanisms underlying AML and the reasons for the difficulties of treating patients with AML have only partly been unravelled. The large difference in outcome between patients with/without Down syndrome suffering from AML-M7 remains to be understood. The various mechanisms of drug resistance certainly play a role in the moderate outcome of patients with AML after intensive chemotherapy. Novel targeted therapies may hopefully improve treatment when combined with the conventional chemotherapeutic approaches.

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