Acute Myelogenous Leukaemia

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Acute myelogenous leukaemia is the result of a malignant transformation of a primitive cell in the bone marrow. The neoplastic transformation imparts a growth and/or survival advantage to the cell. Leukaemic cells fill the haematopoietic cords of marrow. The functional result of this alteration is to impair blood cell production that normally occurs in the marrow, leading to a profound decrease in normal red cells (anaemia), white cells (leucopenia) and platelets or thrombocytes (thrombocytopenia) in the blood (Lichtman and Liesveld, 2000). Untreated, the disease results in death in weeks.

Epidemiology

Acute myelogenous leukaemia (AML) affects slightly more males than females and can occur at any age. The incidence of the disease in the United States (and other industrialized countries) is about one case per 100 000 persons per year during the first 40 years of life. Thereafter, the incidence increases sharply to nearly 20 cases per 100 000 persons per year in octogenarians (Lichtman, 2001).

There are three well-established causes of AML: prolonged or very high exposure to radiation, as was most notable in the Japanese populations near the hypocentre of the atomic bomb detonations in Nagasaki and Hiroshima in 1945; protracted exposure to benzene (more than 20–40 parts per million-years), usually in an industrial setting; and exposure to certain deoxyribonucleic acid (DNA)-damaging chemotherapeutic agents, such as alkylating drugs and epipodophyllotoxins used to treat breast or ovarian cancer, lymphoma and other malignancies. The aforementioned causes, however, account for a very small proportion of cases; most occur without any antecedent causative factor being apparent. Evidence has accumulated pointing to inhaled smoke from tobacco products as a cause of a proportion of cases of AML. Occupational or environmental studies have been neither consequential nor consistent in identifying other exogenous risk factors.

Familial AML is an uncommon phenomenon. Certain inherited conditions are associated with an increased risk of developing AML, such as Down syndrome and Fanconi anaemia. **See also**: Chromosomal genetic disease: numerical aberrations

Pathogenesis

AML is the result of a somatic mutation in a single haematopoietic stem cell or a closely related progenitor cell in the marrow. This acquired alteration in DNA results in the mutation of a proto-oncogene or genes. The latter are a group of normal cellular genes that are usually responsible for encoding proteins that play a role in cell growth, intracellular signalling or programmed cell death (apoptosis). The mutation results in transformation of the proto-oncogene to an oncogene, which encodes too much, too little or a defective cellular protein. This alteration in DNA occurs in one of thousands of stem or progenitor cells and imparts a growth or survival advantage on that cell. The affected cell often has an overt chromosomal alteration: a deletion, an isochromosome, an inversion or a translocation. A translocation of chromosomes is present in nearly half the cases and cryptic translocations are suspected in others. A translocation can join sequences of two genes to create a fusion or chimaeric gene. The chimaeric gene encodes a chimaeric protein, which is often a transcription factor. The target genes for these transcription factors are still unknown in many cases. The encoded protein is referred to as an oncoprotein, the product of an oncogene. This conclusion presumes that there is evidence that chimaeric protein is the central or seminal change in a series of alterations that result in transformation of a normal cell to a neoplastic cell (Gilliland, 2002). **See also**: Apoptosis: molecular mechanisms; Bone marrow; Oncogenes

The somatic mutation probably occurs in a stem cell in most patients, especially adults. In some children or young adults who develop the disease, the mutation occurs in a somewhat more differentiated cell, a progenitor cell, which may have limited differentiation capability confined to the granulocyte and monocyte lineages. In either case, as a result of unregulated cell growth, the neoplastic cell's progeny (the expanded clone of leukaemic cells) replace the normal marrow population of developing blood cells by suppressing the function of residual normal stem cells. The chemical basis for this suppression is not defined. The abnormal cells that accumulate are leukaemic blast cells. These cells are the histopathological evidence for the presence of the disease. At the time of diagnosis, it is estimated that about 10^{11}–10^{13} leukaemic cells have accumulated.

They fill the marrow spaces and enter the blood to varying degrees, perhaps depending on the degree of loss of surface structures that normally anchor immature blood cells to marrow stromal cells. These surface interactions keep developing immature blood cells attached to marrow stromal cells until they have fully matured. The leukaemic blast cell concentration in the blood may range from very low to 30 times the normal total blood cell count. **See also**: Leukaemias and lymphomas

The suppression of normal haematopoietic stem cells prevents their proliferation and differentiation into the several blood cell lineages: red cells, phagocytic white cells (neutrophils and monocytes) and platelets. A profound deficiency of these cells in the blood ensues. The leukaemic blast cells may enter any tissue from the blood but it is uncommon for this infiltration to result in organ dysfunction.

The somatically mutated (neoplastic) stem cell from which the clonal expansion of leukaemic blast cells occurs retains, albeit imperfectly, the ability to differentiate into each blood cell lineage. Some of these offspring or progenitor cells ultimately become committed (differentiate) to a specific lineage such as red cells, neutrophils, platelets or others. Thereafter, they may mature into fully recognizable and functional blood cells, mimicking the development of normal cells. This capability is quantitatively and, often, qualitatively far less than that of normal cells. Moreover, the expression of cellular features is unpredictable and incomplete but the residual capability to differentiate, although anarchic, leads to a panoply of phenotypic variants of AML, including cell populations that have features of developing red cells (erythroleukaemia), developing monocytes (monocytic leukaemia), developing megakaryocytes (megakaryocytic leukaemia) and combinations thereof. In addition to this desultory, incomplete and imperfect maturation, the cells that appear to be residual red cells, white cells and platelets are derivatives of the neoplastic clone and, thus, some cells may reach nearly normal mature stages. These cells may have structural and functional abnormalities, such as misshapen red cells or white cells and platelets without key internal organelles or their contents. The degree of mimicry of normal blood cell development is grossly insufficient to maintain well-being.

If the patient is not treated, leukaemic cells accumulate further and functional cells decrease further leading to spontaneous haemorrhage from severe platelet deficiency or infection from deficiency of phagocytic white cells that provide the principal antimicrobial defences. **See also**: Blood cell: lineage restriction

Clinical Features

The major effects on the patient include a loss of the sense of well-being and sequelae of the decreased blood cell counts: pallor, fatigue, shortness of breath on exertion as a result of anaemia, easy bruising, bleeding from the nose or the gums, scattered pinhead-sized skin haemorrhages (petechiae), prolonged bleeding from minor cuts as a result of a decreased platelet count, minor pyogenic infections of the skin or of cuts and poor wound healing as a result of deficiencies in neutrophils and monocytes (phagocytes). Occasionally, more severe bleeding from the genitourinary, gastrointestinal or bronchopulmonary tract or into the central nervous system may be present. Major infections such as sinusitis, pneumonia, septicaemia or meningitis can be present initially but are more likely to occur after treatment has been instituted, at which time residual functional blood cells are decreased even more profoundly.

Loss of appetite, mild weight loss and fever may be present. The spleen and liver may be slightly enlarged in a minority of patients. Leukaemic blast cells may accumulate in the skin or subcutaneous tissues.

Various infiltrative skin lesions referred to as leukaemia cutis may result. Larger masses in the head and neck region in particular, but occasionally in other sites, may be present and are referred to as granulocytic sarcomas. Occasionally, mysteriously, they may be the first sign of the disease, and overt marrow involvement may follow months later.

Laboratory Findings

A decrease in the blood haemoglobin (red cell) concentration (anaemia) and in blood platelet concentration (thrombocytopenia) are nearly constant features at the time of diagnosis. The total white blood cell count is below normal in about half of the cases but in others may be normal or raised, occasionally to as much as 30 times the normal value. In the latter case, the excess cells are usually leukaemic blast cells or blasts admixed with immature derivative cells. Even in patients with very low total leucocyte counts, the differential white cell count will contain blast cells, which are not present in normal blood.

The microscopic examination of stained films of a marrow aspirate and stained sections of the percutaneous biopsy of marrow, usually obtained from the rim of the pelvis (crest of the ilium) using local anaesthesia, identifies leukaemic blast cells, the hallmark of the disease. Any of three characteristics permits the designation of the blast cells as being myelogenous (myelocytic) in contrast to lymphocytic: (1) The presence of Auer rods in the cytoplasm of the blast cells, linear ovoid structures that are about 1.0 μm in length; these abnormal cytoplasmic inclusions are the result of fusion of primary granules into attenuated elliptical structures. (2) A positive reaction within the cytoplasm of the blast cells to the histochemical stains for peroxidase, Sudan black B or certain esterases. (3) The presence of cluster of differentiation (CD) antigens on the surface of the blast cells that characterize myeloblasts, such

Table 1 Some cytogenetic abnormalities associated with AML

Alteration	Key genes affected
t(8;21)	*AML1-ETO*
inv(16)	*CBFβ-MYH11*
t(15;17)	*PML-RARα*
t(9;11)	*MLL-AF9*
t(9;22)	*BCR-ABL*
t(11;19)	*MLL-ENL*
t(6;9)	*DEK-CAN*
t(3;21)	*AML1-EAP*
t(3;21)	*AML1-EVI1*
t(12;21))	*TEL-AML1*
t(12;22)	*FUS-ERG*
Trisomy 8	ND
Trisomy 21	ND
−7 or del 7q	ND
−5 or del 5q	ND
−Y	ND

Note: t, translocation; inv, inversion; del, deletion; q, long arm of chromosome; ND, not defined.

as CD11, CD13, CD15 and CD33. The latter features are usually detected with corresponding monoclonal antibodies labelled with a fluorescent conjugate using a flow cytometer that detects, through laser beam activation, the fluorescence of antibody-tagged cells (Casasnovas *et al*., 2003).

The marrow cells are also examined by light microscopy for chromosomal changes that occur in about 50% of cases and can be demonstrated with special techniques in a high proportion of the remainder. The cytogenetic changes may be primary and result in the key mutation that leads to the formation of an oncogene, or may in some cases be secondary. Some correlations occur between the phenotype expressed by the leukaemic cells and the cytogenetic change in those cells, which is especially true in the case of translocations, whereas in other cases the same cytogenetic change may be present in different morphological variants of AML. **Table 1** contains some examples of cytogenetic changes in AML (Visani *et al*., 2000).

Special Features of Morphological Variants

Most cases have cell types that are similar to myeloblasts, sometimes with maturing cells in the neutrophil series, designated acute myeloblastic leukaemia, or a mixed population of myeloblasts and monocytic cells, designated AML. An important subset of patients are those with a translocation between chromosomes 15 and 17 that produces a chimaeric or fusion gene involving parts of the two genes *PML* and *RARα*. Some patients have variant translocations, but *RARα* on chromosome 17 is involved (Grunewade and Lo Coco, 2002). These patients have leukaemic cells that are phenocopies of normal promyelocytes, cells that are the second stage of maturation in the development of the segmented neutrophil, the most prevalent normal white blood cell. This variant is designated as acute promyelocytic leukaemia. This variant is associated with the release of the heavily granular promyelocytes of a procoagulant from the granules and an anti-anticoagulant that predispose the patient to intravascular consumption or destruction of coagulation proteins resulting in a tendency to haemorrhage. This variant is unique in its response to the use of an analogue of vitamin A, all-*trans*-retinoic acid or arsenic trioxide (see Treatment).

Cases of AML in which the cells have features of monocytes are prone to have skin and gingival involvement, enlargement of lymph nodes and spleen; leukaemic infiltration of the meninges; and release of tissue factor, a procoagulant which favours intravascular coagulation. Cases in which the leukaemic cells have features of megakaryocytes, the marrow cells from which platelets are derived, are associated with an intense fibroplasia in the marrow stimulated by a series of fibroblast growth factors (e.g. transforming growth factor β, basic fibroblast growth factor, platelet-derived growth factor), which are constituents released from the granules in the cytoplasm of leukaemic megakaryocytes, normally destined to be essential components of platelet granules. Cases in which the cells have features of basophils, mast cells or eosinophils are extremely uncommon.

The Spectrum of Clonal (Neoplastic) Haemopathies

AML is the most rapidly progressive in a spectrum of haematopoietic stem cell or progenitor cell neoplasms (see **Table 2**). Each of the less rapidly progressive syndromes is susceptible to genomic instability in the transformed stem cell (Lichtman, 2000a). These additional genetic changes lead to progression to AML. This risk varies depending on the clonal haemopathy. In the case of treated clonal polycythaemia (vera), clonal thrombocythaemia and clonal sideroblastic anaemia, the risk may be in the range of 10–20%, whereas in the case of chronic myelogenous leukaemia it is nearly inevitable, except in the small proportion of patients who are cured by allogeneic bone marrow transplantation or who succumb from an unrelated cause. The progression to acute leukaemia may occur in months or years, or occasionally after decades of previous illness. Patients with oligoblastic myelogenous leukaemia have a subacute course. This type of leukaemia is referred to as myelodysplasia, an unfortunate misnomer that has

Table 2 Clonal haemopathies

Minimal deviation neoplasms (no leukaemic blast cells in marrow)
Clonal polycythaemia
Clonal thrombocythaemia
Clonal sideroblastic anaemia
Clonal bictopenias or tricytopenias
Slower progression leukaemias (very low proportions of leukaemic blast cells marrow)
Chronic myelogenous leukaemia
Idiopathic myelofibrosis (agnogenic myeloid metaplasia)
Intermediate progression leukaemias (low proportions of leukaemic blast cells in marrow)
Oligoblastic leukaemias (syn. refractory anaemia with excess blasts or myelodysplastic syndrome) subacute myelomonocytic leukaemia
Rapid progression leukaemias (higher proportions of leukaemic blast cells)
AML including all morphological (about 10) and genetic variants (about 100)

been applied because the patients have more dysmorphic changes in their blood cells than patients with polyblastic (acute) leukaemia (Lichtman, 2000b). Oligoblastic myelogenous leukaemia is a neoplasia with a very high morbidity and mortality rate. Oligoblastic or smouldering leukaemia can progress to a clinical state more closely simulating AML. This occurs in at least 30% of patients. The mechanisms of clonal instability (additive mutations and progression of disease severity) are not defined but such knowledge and the ability to interrupt the process would have great usefulness.

Treatment

The principal form of treatment is intensive multidrug therapy, usually administered over a period of about 7–10 days (Lichtman and Liesveld, 2000). Cytarabine and an anthracycline antibiotic are two drugs used most commonly for initial treatment (**Table 3**). The goal of such treatment is to decrease the body burden of leukaemic cells. If this can be accomplished, usually in the order of a three-log decrease in the presumptive trillion cell burden, the marrow is made profoundly hypocellular (aplastic). In this setting, inhibitory effects on the residual normal stem cells are relieved and normal haematopoiesis is reconstituted in most patients; nearly normal concentrations of all blood cells are restored over a period of 4–6 weeks. One exception to this approach is the responsiveness of acute promyelocytic leukaemia to retinoic acid and to arsenic trioxide. The former has been used more extensively and induces remission in a high proportion of cases. Chemotherapy must be used concurrently, however, to prevent an early relapse.

In some cases, even after two or three repetitive cycles of treatment, the leukaemic cell population is not decreased sufficiently to permit reconstitution of blood cell production. Such patients are refractory to therapy. If the induction of remission is not followed by intensive therapy (continuation or consolidation treatment), relapse will occur. Even with consolidation therapy, relapses are common in the ensuing months or within a few years. Many variables have been associated with drug responsiveness but age of the patient is one of the most compelling. Youth is associated with a higher remission rate and a longer duration of remission. The remission rate and the cure rate decrease with each succeeding decade of life and this is particularly problematic because the incidence of the disease increases dramatically after age 50 years.

Resistance to chemotherapy is a serious impediment to initial or to long-term remission and cure. The identification of genes and their products that mediate drug resistance has provided a new understanding of the problem and strategies to overcome it. One of several such phenomena is the expression and overexpression of a membrane glycoprotein that mediates the outward transport (pumping) of chemotherapeutic agents of several classes. The gene that encodes the glycoprotein is *MDR*, an abbreviation for multidrug resistance. Overexpression of the protein prevents the accumulation of high intracellular concentrations of several important drugs used in treatment. This factor may account, in part, for the higher state of resistance in older individuals with the disease, in whom higher degrees of expression of *MDR* occur.

Allogeneic stem cell transplantation can be used to treat patients who have a histocompatible donor (Negrin and Blume, 2000). This is usually not used in older patients, perhaps over age 50 years, because of the high rate of intolerance to the procedure. Stem cell transplantation is considered for patients who have cytogenetic or other findings that have been associated with a poor outcome of treatment or relapse after chemotherapy-induced remission. A tissue-type matched donor is required. Usually, this is a sibling. Stem cell transplantation permits very intensive therapy, often in combination with total body radiation and high-dose chemotherapy. Blood and immune cell production is reconstituted by the allogeneic stem cells. The procedure may have several serious adverse effects, especially graft-versus-host disease, and the risk of opportunistic infections by a variety of microorganisms (e.g. *Pneumocystis carinii,* various fungi and viruses). Graft-versus-host disease results from an immune attack by donor lymphocytes against host tissues, especially skin, gastrointestinal tract and liver. It ranges from mild and transient to chronic and unrelenting. The older the

Table 3 Some drugs used in the treatment of AML

Antitumour antibiotics
These drugs interact directly with the DNA in the nucleus of cells, interfering with cell survival
Daunorubicin (Daunomycin, Rubidomycin, Cerubidin, Daunoxome)
Doxorubicin (Adriamycin, Rubrex)
Mitozantrone (Novantrone)
Idarubicin (Idamycin, Zavedos)
Antimetabolites
These are chemicals that are very similar to natural building blocks of DNA or ribonucleic acid (RNA). They are changed from the natural chemical sufficiently so that, when they substitute for it, they block the cell's ability to form RNA or DNA, preventing the cell from growing
5-Azacytidine (Mylosar)
Cytarabine (cytosine arabinoside, Ara-C, Cytosar)
Cladribine (2-chlorodeoxyadenosine, Leustat)
Fludarabine (Fludara)
Hydroxyurea (Hydrea)
6-Mercaptopurine (Purinethanol, Puri-Nethol)
Methotrexate (Maxtrex)
6-Thioguanine (Lanvis)
DNA repair enzyme inhibitors
These drugs act on certain proteins (enzymes) that help to repair injury to DNA. They prevent the enzymes from working and make the DNA more susceptible to injury
Etoposide (VP-16, Vepesid, Etopophos)
Teniposide (VM-26, Vumon)
Topotecan (Hycamtin)
DNA synthesis inhibitors
These drugs react with DNA to alter it chemically and prevent it from permitting cell growth
Carboplatin (Paraplatin)
Monoclonal Antibodies
Engineered in the laboratory to attach to leukaemic cells via specific surface target. Antibody carries potent cell toxin or radioisotope. Designed to minimize toxicity on tissues other than marrow
Gentuzumab ozogamicin (Mylotarg)
Cell maturing agents
Act to induce maturation and apoptosis of leukaemic promyelocytes, which results in depopulation of leukaemic cells and release of the inhibition of normal haematopoietic stem cells. This effect usually restores normal blood cell development. Effects are transient if not accompanied or closely followed by cytotoxic therapy
Tretinoin (all-*trans* retinoic acid, Vesanoid)
Arsenic trioxide (Trisenox)

recipient, the more likely the reaction is to be disabling. The benefit of the transplant may include an effect referred to as graft-versus-leukaemia reaction, which is mediated, also, by lymphocytes of the donor. This effect acts to suppress reexpression of the malignant clone. It is not as constant a feature after transplantation of acute compared with chronic myelogenous leukaemia, but may be important in some patients. **See also**: Transplantation of haematopoietic stem cells

As most patients do not have a matched donor, autologous stem cell infusion has been used to rescue patients after very intensive therapy. Stem cells are harvested from the patient after they have achieved remission following chemotherapy. The stem cells from marrow or blood are frozen and reinfused after intensive therapy with total body radiation and/or chemotherapy. This approach has been referred to as autologous transplantation, but the graft-versus-leukaemia reaction does not occur since there

are no major or minor histocompatibility differences. Purging of any residual leukaemic cells in the recovered stem cells can be performed before reinfusion.

The intensive therapy undertaken to attempt to induce remission leads to a period in which blood cells are further decreased and transfusion of red cells and platelets is required. Infection is common and requires antibiotic therapy. Other serious complications can develop and this period between intensive therapy and restoration of blood cell production requires artful and skilled management.

Immunotherapy has been or is being introduced as an additional approach to control the disease. These techniques include the use of monoclonal antibodies that are conjugated with toxins such as calicheamycin or a radioisotope. These antibodies are targeted to CD antigens on the leukaemic cell surface. The use of T lymphocytes or natural killer cells that can be induced to attack leukaemic cells may be forthcoming. The use of specific antigens on leukaemic cells that can be used to 'vaccinate' patients to heighten the response of immune cells to the tumour is also under study. **See also**: Monoclonal antibodies: therapeutic uses

Remission lasting for at least 5 years is considered likely to represent a cure of this disease. This result occurs in about 30% of children and about 10% of adults.

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