

Epidemiology, pathogenesis, and etiology of acute leukemia

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Epidemiology and incidence

Acute myeloid (AML) and acute lymphocytic leukemia (ALL) are rare diseases, accounting for approximately 1.3% and 0.4% of all new cancer cases in the US. While the overall incidence of leukemia has been stable since 1975 (13 new cases/ 100,000 in 1975 and 14 new cases/ 100,000 in 2012) [1], the rates for new AML and ALL cases have been rising on average by 2.2% and 0.6%, respectively over the last decade [2,3].

International and US statistics

The annual number of new cases/100,000 was 1.7 for ALL and 4.0 for AML in the US [2,3], and similar rates are observed in other industrialized countries such as Germany with 5.2 new AML cases and 1.6 ALL cases in 2010 [4], and UK with 4.5 AML cases and 1.0 ALL cases [5,6]. In other words, in these three countries AML and ALL account for approximately 35,000 new cancer cases per year. With an estimated 5-year survival rate of 25.9% for AML and 67.5% for ALL [2,3], these diseases were responsible for approximately 12,000 deaths in 2015 in the US alone.

Age, sex, and ethnicity-related differences

Both forms of acute leukemia are strongly related to age, but in an inverse manner. While ALL has its peak in childhood, AML is more common in the elderly (Figure 2.1). Accordingly, the median age at diagnosis for AML is 67 years and 14 years for ALL [2,3].

There is a predilection for men with AML (4.8 versus 3.3 new cases) while in ALL, there is no gender difference (1.9 new cases in men and 1.5 in women) [2,3]. Caucasians have the highest incidence of AML while persons descending from native North Americans have the lowest incidence. For ALL, people of Hispanic origin have the highest incidence while the lowest is found in people of color [2,3].

Biology and pathogenesis of acute leukemia

Both myeloid and lymphocytic acute leukemia arise from genetic lesions in hematopoietic progenitor cells. The lineage of the progenitor, in which the lesion occurs, determines the type of leukemia (lymphoid versus myeloid), but there is less security about the exact lineage-specific progenitor cells

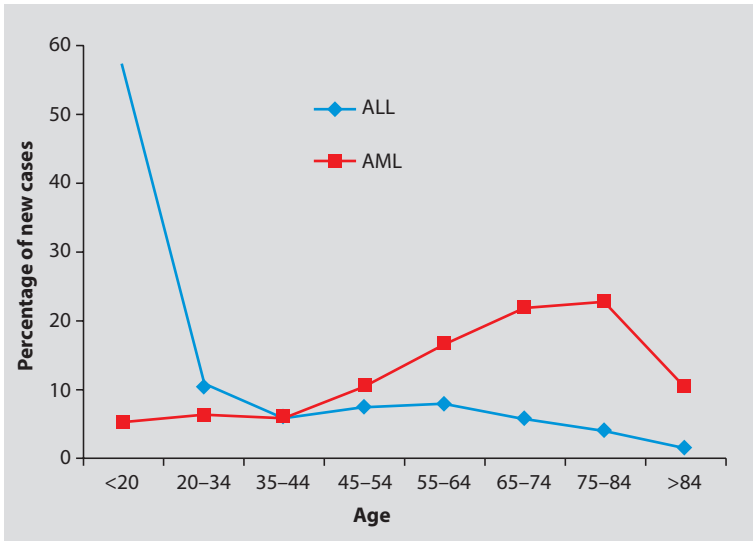


Figure 2.1 Age-related incidence of acute leukemias. Acute lymphocytic leukemia has its peak incidence in childhood, while acute myeloid leukemia is a disease mainly of the older age. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia. Adapted from © National Cancer Institute, 2016. All rights reserved. National Cancer Institute, SEER [2,3].

that are affected. Generally, these transformed cells are termed leukemia-initiating cells (LIC) but they do not necessarily comprise hematopoietic stem cells. These LICs represent a small minority within the whole leukemic cell population; both have the ability of self-renewal and modest differentiation (for example, as reviewed in reference [7]). They can be identified by functional characteristics (ie, repopulating potential in mice) and phenotyping of cell surface markers (for example, CD34, CD38, and human leukocyte antigen-DR [HLA-DR]). The leukemic bulk instead, forming the majority of tumor burden, does not have stem cell qualities and hence has no ability to engraft in mice or cause relapse. However, this bulk is responsible for the symptoms of the diseases: overgrowth of the bone marrow with depletion of healthy progenitors and consecutive hematopoietic insufficiency with (pan-)cytopenia and occasional hyperleukocytosis in the peripheral blood, resulting in organ ischemia due to 'white clots' comprising leukemic blasts and subsequently organ failure.

The genetic lesions that cause the malignant transformation are less well understood. The identification and unraveling of the functional consequences of the translocation (15;17) in acute promyelocytic leukemia (APL) has sparked the hope that for other forms of acute leukemia, especially those with recurrent aberrations such as AML with t(8;21) or ALL with t(9;22), similar genetic lesions could be identified that explain the pathophysiology of the disease and may be targeted by specific therapies. In APL, a balanced translocation between chromosomes 15 and 17 leads to a fusion gene called promyelocytic leukemia-retinoic acid receptor α (*PML-RAR α*) gene [8]. The resulting protein comprises a transcription factor that is fused to co-repressors of transcription. As a consequence, affected cells are unable to differentiate into neutrophil granulocytes and remain at the stage of promyelocytes. The systemic administration of high doses of retinoic acid binds the RAR part of the fusion protein, leading to conformational changes with dispensation of the co-repressors, thus re-establishing transcription and differentiation [9].

However, for most cases of AML one single genetic defect is not sufficient for leukemic progression; instead a series of genetic events is required. These events target genes that are involved in different cellular processes, for examples mutations in Fms-like tyrosine kinase 3 (*FLT3*),

K-RAS, or *c-kit* [10], and are supposed to confer a proliferative advantage, while other mutations, for example in *CEBPA* [11], impair hematopoietic differentiation. However, further mutations have been identified that affect genes involved in epigenetic regulation (*IDH*, *DNMT3A*, or *ASXL1* in myelodysplastic syndrome [MDS]-related AML [12]). On average, 13 genes are mutated in AML, only 5 of which are recurrent and these mutated genes can be allocated to one of 9 groups associated with certain biological features (fusion genes, myeloid transcription factors, tumor suppressors, spliceosome, DNA modification, NPM1, chromatin modifiers, cohesins, and signal transduction) [13].

Similarly, in ALL genetic lesions can be found in the vast majority of cases [14]. Best known is the translocation (9;22)(q34;q11.2), which occurs in approximately 15–25% of patients (Ph+ ALL) [14]. This translocation results in the creation of the fusion gene *BCR-ABL1* and confers a bad prognosis. Recently another form of ALL has been identified, which displays a gene expression profile similar to that of Ph+ ALL but without the aforementioned translocation and hence without *BCR-ABL1* [15,16]. This type of ALL is characterized by a bad prognosis similar to Ph+ ALL and was therefore named Ph-like ALL [16]. Genetic characterization has identified deletions in transcription factors relevant for B-cell development (eg, *IKZF1*, *EBF1*, and *VPREB1*) in more than 80% of cases, but kinase-activating alterations were also regularly found, for example involving, among others, *ABL1*, *EPOR*, *CSF1R*, or *PDGFRB* to name a few (as reviewed in reference [17]). In general, these alterations result in, as with *BCR-ABL1*, an activation of intracellular downstream signaling via Janus kinases (JAK; further enhanced by occasional activating mutations in JAK1 or 2), which in turn lead to cytokine-independent proliferation via activation of signal transducer and activator of transcription 5 [STAT5]. In hypodiploid ALL, distinct genetic lesions have been identified that differ with respect to the severity of aneuploidy [18]: while near-haploid ALL (24–31 chromosomes) have acquired mutations in receptor tyrosine kinases, Ras and *IKZF3*, low-hypodiploid ALL (32–39 chromosomes) have a high frequency of TP53 mutations. Both subtypes show a high activation of Ras and PI3K, which results in the activation of pro-survival and anti-apoptotic pathways and offers targets for therapeutic intervention.

Etiology of acute leukemia

Even though the exact genetic malfunctions in the hematopoietic stem cells that result in malignant transformation are not exactly understood, several risk factors for the development of acute leukemia have been identified. However, the majority of patients with acute leukemia do not meet any of these conditions.

Exposure to ionizing radiation

Ionizing radiation can result in DNA mutations, deletions or translocations by inducing double strand breaks in hematopoietic stem cells in a dose-dependent manner. The leukemogenic effect of ionizing radiation has long been identified, mainly because of the increased incidence of both AML and ALL in atomic bomb survivors [19] and radiologists that were exposed to high levels of radiation [20]. Similarly, radiation used in the treatment of cancers has been made responsible for the development of acute leukemia [21].

Exposure to benzene

Exposure to benzenes has been known to increase the risk for the development of AML and MDS for several decades [22]. There seems to be a dose dependency, with lower levels of benzene increasing the risk for MDS but not for AML [23], but no definite threshold has been defined that can be considered safe. There is also an association with development of ALL [24], and in many countries, acute leukemia resulting after benzene exposition during work has been recognized as an occupational disease.

Way of living

Besides exposure to chemicals, the way of living can affect the risk for the development of AML and ALL. While the pathophysiological mechanisms are unknown, it has been shown that being overweight [25] and also smoking increases the risk for acute leukemia [26,27]. There is no clear evidence for the role of alcohol intake in adult AML or ALL [28,29], but parental alcohol consumption might increase the risk for the development of childhood leukemia [30,31].

Genetic conditions

There are several genetic disorders that have predominantly systemic manifestations but are also associated with the development of acute leukemia such as Down syndrome [32] and Li Fraumeni syndrome [33]. In addition, inherited bone marrow failure syndromes such as Fanconi anemia and Shwachman-Diamond syndrome pose a predisposition for the development of myeloid neoplasias and acute leukemia [33]. Rare forms of familial acute leukemia also exist, in which certain genes are affected and the families display minor or sometimes no prior hematopoietic abnormalities. In some of these cases, genes are involved that have been associated with de novo AML (for example, *RUNX1*, *CEBPA*, *ETV6*, and *TERT*) but there are also genes that predispose a person to ALL (for example, *SH2B3* and *PAX5*) [34].

Preceding blood and marrow disorders: secondary acute myeloid leukemia

Malignant, but also several non-malignant, myeloid disorders increase the risk for the development of AML, which is then called a secondary AML (sAML). Best known is AML secondary to MDS, and the World Health Organization (WHO) classification recognizes AML with myelodysplasia-related changes as a distinct entity [35]. MDS is a highly diverse group of diseases, and the risk of developing AML varies significantly between the different subgroups. In general, the risk of MDS can be assessed by the morphological subtype (where forms with an increase in blast counts RAEB-1 (5–9%) and RAEB-2 (10–19%) have the lowest survival [36]), but is more accurately reflected by the revised international prognostic scoring system (IPSS-R [37]), which takes into account cytopenias, blast count, and cytogenetics (Table 2.1). With this score, it is possible to estimate the survival probability and to identify groups at a very high risk for transformation into AML (for example, in the group of very high risk patients 25% will develop AML within 0.7 years [37]). Other myeloid neoplasias that pose a risk for transformation into AML include essential thrombocytopenia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). Chronic myeloid leukemia (CML) in blast crisis, although resembling AML, represents a different entity. The risk for the

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blasts (%)	≤ 2		>2–<5		5–10	>10	
Hemoglobin	≥10		8–<10	<8			
Platelets	≥100	50–<100	<50				
ANC	≥0.8	<0.8					

Table 2.1 The International prognostic scoring system (IPSS-R) for assessment of individual risk in patients with myelodysplastic syndromes. For each applicable feature, the appropriate points are given, which add up the respective risk category (very low ≤1.5, low >1.5–3, intermediate >3–4.5, high >4.5–6, and very high >6). ANC, absolute neutrophil count. Reproduced with permission from © American Society of Hematology, 2012. All rights reserved. Greenberg et al [37].

development of AML in the aforementioned myeloproliferative diseases is approximately 5% [38], but patients at risk cannot be adequately identified, as scoring systems (for example, the dynamic international prognostic scoring system [DIPPS] in PMF) estimate survival in general [39]. Non-malignant diseases can increase the risk for the development of acute leukemia, but the reasons for this are unclear. Among the most common of such diseases are paroxysmal nocturnal hemoglobinuria (PNH [40]) and severe aplastic anemia [41]. However, most patients with these diseases suffer from complications other than the development of acute leukemia but this might change with the advent of more potent treatments (for example, eculizumab for PNH), which will increase survival by the reduction of non-malignant complications (such as thrombosis) but with an unknown effect on the development of sAML.

Prior chemotherapy

While there is no clear evidence that ALL may arise as a consequence of preceding chemotherapy for other cancers, the risk of AML is clearly increased in patients who received chemotherapeutic treatment, for example for breast cancer [42] and Hodgkin lymphoma [43], usually within 3–5 years. As such, cytotoxic agents commonly used in the treatment of malignant diseases have been implicated with therapy-related AML (t-AML), especially alkylating agents (for example, melphalan, busulfan, cyclophosphamide, and carbo- and cisplatin) and topoisomerase II

inhibitors (for example, etoposide and doxorubicin) [44]. The majority of t-AML represents with chromosomal abnormalities, which are often unfavorable (for example, complex aberrant 26.9% versus 11.3% in de novo AML [45]) and after topoisomerase II inhibitor treatment mutations involving the MLL gene (*11q23*) are frequently observed [46]. This later form usually develops much quicker (within 1–2 years after initial treatment). The WHO recognizes t-AML as a distinct entity [44].

Granulocyte colony-stimulating factor (G-CSF), given as an adjunct in patients receiving chemotherapy or to stimulate expulsion of stem cells into the peripheral blood for harvesting for either autologous or allogeneic stem cell transplantation, may result in an increased risk of AML and MDS. One large meta-analysis [47] found that in patients treated with chemotherapy, the application of G-CSF increased the risk of development of AML or MDS from 0.4% to 1.9%, however the general mortality in this group declined by 3.4%.

Autoimmune conditions

Patients with autoimmune disorders (for example, rheumatoid arthritis) receiving immunosuppressants have an increased risk for the development of MDS or AML, similarly to t-AML. However, as doses of immunosuppressants including chemotherapy (methotrexate [MTX] and cyclophosphamide) are lower in these patients, the risk of therapy-related myeloid neoplasias is also lower.

Viruses

For AML, there is no evidence for viral infection in the pathogenesis. In certain subsets of acute lymphocytic leukemia, viral infections have been associated with the pathogenesis, for example of adult T-cell leukemia-lymphoma (caused by the human T-lymphotropic virus type I (HTLV-I) [48]) and Burkitt lymphoma/leukemia, which is associated with Epstein-Barr virus (EBV) but also with immunosuppression (for example, acquired immune deficiency syndrome [AIDS]) and co-infection with malaria (see review in reference [49]).

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