Acute Myeloid Leukemia: Epidemiology and Etiology

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Acute myeloid leukemias (AMLs) are infrequent, yet highly malignant neoplasms responsible for a large number of cancer-related deaths. The incidence has been near stable over the last years. It continuously shows 2 peaks in occurrence in early childhood and later adulthood. With an incidence of 3.7 per 100,000 persons and an age-dependent mortality of 2.7 to nearly 18 per 100,000 persons, there is a rising awareness in the Western world of AML’s special attributes resulting from an ever-aging population. To objectively describe epidemiologic data on this patient population, recent publications were evaluated to make transparent the current trends and facts. A review of the literature is presented, reflecting highlights of current research with respect to AML etiology. To estimate outcome and discuss informed treatment decisions with AML patients of different age groups and different biologic risk categories, it is mandatory to consider that the outcome results reported in clinical trials were until now heavily biased toward younger patients, whereas the overall dismal prognosis documented in population-based studies most likely reflects the exclusion of older patients from aggressive treatment. The etiology for most cases of AML is unclear, but a growing knowledge concerning leukemogenenic agents within chemotherapy regimens for other malignancies is already available. This includes specific associations of the most frequent balanced translocations in AML, including the “good-risk” abnormalities comprised by the core binding factor leukemias (i.e., AML with the translocation (8;21) and inversion of chromosome 16, and acute promyelocytic leukemia with the translocation (15;17)). In contrast to these genetic alterations, epigenetic lesions, e.g., promoter silencing by hypermethylation of the p15/INK4b and other genes, are increasingly recognized as important in the pathogenesis of AML. Cancer 2006;107:2099–107. © 2006 American Cancer Society.

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Acute leukemias are rare diseases, but have a disproportionally large effect on cancer survival statistics.1 Acute myeloid leukemia (AML) is the most common type of leukemia in adults, yet continues to have the lowest survival rate of all leukemias. Although rates have improved remarkably in the younger age group, the prognosis in older patients continues to be very poor.2,3

Incidence

The American Cancer Society estimates that 31,500 individuals in the U.S. will be diagnosed with 1 form of leukemia annually. Approximately 21,500 patients will die of their disease.4,5 Although the incidence of acute leukemias accounts for <3% of all cancers, these diseases constitute the leading cause of death due to cancer in children and persons age <39 years.4,6

AML accounts for approximately 25% of all leukemias in adults in the Western world, and therefore is the most frequent form of
leukemia. Worldwide, the incidence of AML is highest in the U.S., Australia, and western Europe. The age-adjusted incidence rate of AML in the U.S. in the years 1975–2003 was approximately 3.4 per 100,000 persons (2.5 per 100,000 persons when age-adjusted to the world standard population). The American Cancer Society estimates that 11,930 men and women (6350 men and 5580 women) in the U.S. will be diagnosed with AML in 2006.

Age
Leukemia is the most common cancer diagnosis in children age <15 years, with an overall incidence of 4.3 per 100,000 persons in the U.S. However, in this age group acute lymphocytic leukemia (ALL) is approximately 5 times more common than AML, thereby accounting for approximately 76% of all childhood leukemia diagnoses. Conversely, AML comprises only 15% to 20% of cases in patients age ≤15 years. The peak incidence rate occurs in the first year of life and then decreases steadily up to the age of 4 years, at which point it remains relatively constant throughout the years of childhood and early adulthood.

AML is therefore primarily a disease of later adulthood. The distribution of the proportion of prevalent cases of all leukemias in the U.K. shows that 42.8% of patients are age >65 years. Patients newly diagnosed with AML have a median age of 65 years. AML is rarely diagnosed before the age of 40 years; thereafter, the incidence increases progressively with age. From 2000 to 2003, the U.S. incidence rate in people age <65 years was only 1.8 per 100,000 persons, whereas the incidence rate in people age ≥65 years was 17 per 100,000 persons (Fig. 1). As shown in Figure 1, a slight decrease in the incidence of AML in patients age >85 years in the U.S. population raises the question of whether a lack of published data regarding this phenomenon presents an artifact due to underdiagnosed AML cases in the oldest old.

Based on the documented frequent progression of myelodysplastic syndromes (MDS) to AML, an increased incidence of MDS with age appears to partly explain both the high incidence and poor prognosis of AML in the elderly. Because an increasing blast count in MDS leads to higher mortality without reaching the definition of AML, a distinction between the 2 entities of myeloid disorders may be primarily semantic. The common AML subtype in the elderly shares characteristics with AML that follows MDS, Fanconi anemia, and alkylating agent chemotherapy, and occurs in an estimated 10% to 15% of AML in younger patients. It has been referred to as MDS-related AML and is characterized by common cytogenetic abnormalities shared with MDS, and frequent multilineage dysplastic morphology in residual hematopoietic precursors. By contrast, AML with genotypes typical of younger patients, true de novo AML, has an approximately flat incidence throughout life, also in progressive age groups. Approximately 5% of elderly patients with AML are estimated to belong to the true de novo AML group, which is consistent with the incidence in younger patients.

An increased incidence of unfavorable cytogenetics contributes to poor outcome in patients age >56 years, and, within each cytogenetic risk group, treatment outcome deteriorates with age.

Although incidence rates for AML have been reported to be nearly stable over time among the different age groups, there was a slight increase noted among the oldest group.

Gender and Ethnicity
The incidence of AML varies with gender and race. In the Surveillance, Epidemiology, and End Result (SEER) database for children ages 1 to 4 years there was an incidence rate of 0.8 per 100,000 persons for boys and for girls. In the first few years of life, the incidence of AML in whites is 3-fold higher than in blacks; however, blacks have slightly higher rates of AML among children age ≥3 years.

AML in adults has a slight male predominance in most countries. In 2000–2003, the age-adjusted incidence rate of AML in the U.S. was 3.7 per 100,000 for both sexes, 4.6 per 100,000 for males, and 3.0 per 100,000 for females. The incidence rate of U.S. males is substantially higher than the incidence rates reported for males in all other countries.

In the U.S. in 2000, AML was more common in blacks than in whites. However, during 2000 to 2003, the incidence of AML for blacks (3.2 per 100,000 persons) was lower than for whites (3.8 per 100,000 persons).
Mortality

Untreated AML is a uniformly fatal disease. Although it is possible to support patients for a certain period (median survival, 11–20 weeks), they ultimately die of the leading complications associated with bone marrow failure (i.e., infection and hemorrhage). Most patients seek medical attention for symptoms related to anemia, infection, or bleeding, and those patients typically require immediate therapeutic intervention. Other patients are not candidates for cytotoxic therapy, mainly because of older age and/or poor performance status or other active severe medical comorbidities that complicate their care. In such settings, a supportive strategy may be most appropriate. Firm stratification criteria for decision-making in this setting are not uniformly established.

After long-term increases or mostly level trends that date from the 1930s, death rates for all leukemias were reportedly decreasing in the 1990s in the U.S. and Europe. From 2000 to 2003, the U.S. age-adjusted mortality rate of AML was 2.7 per 100,000 persons. As is the case with incidence, the mortality associated with AML varies with age, gender, and race. Mortality rates in the U.S. appear to increase with age because the age-adjusted mortality rate shows its peak at 17.6 per 100,000 persons in people ages 80 to 84 years.

The mortality rate for males is higher than that for females, with the U.S. age-adjusted mortality rate at 3.5 per 100,000 for males and 2.2 per 100,000 for females (2000–2003). AML mortality is greater in whites than in blacks. The U.S. age-adjusted mortality rate was 2.7 per 100,000 for whites and 2.2 per 100,000 for blacks in the year 2000. It is estimated that approximately 7,800 adults will die annually of AML in the U.S. The overall U.S. survival rate associated with AML from 1996 to 2002 was 21.7%. Figure 2 depicts 5-year survival rates stratified by age. The 5-year relative survival rate was highest for those who were younger and female. In AML, however, as opposed to the entire group of leukemias, blacks had a slightly better 5-year survival rate than whites (21.5% vs. 19.8%).

A recent study reported that the 5-year survival rate of those age ≤55 years was 23%, whereas the corresponding rate for those age >55 years was 11%. Survival rates have increased in the last decade among this younger group (from 9% in the 1980s to 35% in the 1990s), but have not changed in the older group, who therefore pose the biggest challenge for achieving a therapeutic success.

In a large recent Italian population-based study (n = 1005), the median survival of patients age >60 years with AML who were treated with either supportive or aggressive therapy was 5 months and 7 months, respectively. In patients age >70 years, the median survival was 4 months, which was, notably, regardless of the type of therapeutic effort. Age has further been shown to be inversely associated with 1) referral to a treatment center and/or inclusion into a clinical trial; 2) tolerance to induction treatment (early death or death during the immediate postchemotherapy phase); and 3) the ability to achieve remission. In older patients (age >60 years), standard induction therapy achieves complete remission in only 30% to 50% of treated individuals. Further, most rates of disease-free survival reported in major clinical studies are above these rates (e.g., 4-year survival rates of up to 42%), yet they too demonstrate quite variable results. The differences in survival results noted among various trials using similar chemotherapy can possibly be explained by the prevalence of negative prognostic characteristics within a study.
population. To understand clinical features and outcomes of that significant number of patients not meeting inclusion criteria for clinical studies, population-based evaluations have found increasing attention. Some results concerning age distribution, treatment decisions, remission rates, and survival in AML do demonstrate significant differences in some of the large clinical investigations. In 1 report, of a total of 170 AML patients, 55% were treated outside a study protocol. Nonstudy patients differed significantly from patients included in clinical trials with respect to age and performance status at the time of clinical presentation, comorbidity, and type of AML. Patients who participated in a clinical trial had a median age of 46 years (range, 16–73 years), whereas those not included were significantly older (median age of 63 years; range, 21–83 years). Survival was significantly better in patients treated in a clinical protocol (median overall survival of 15 months vs. 3.4 months). For survival results in population-based studies, see Table 1. An increase in median survival may possibly, at least partly, be explained by improved supportive care over the past decades.

Late Survivorship
The incidence of and risk factors for the development of late sequelae of treatment in patients who survived for >10 years (median, 15 years) after a diagnosis of childhood AML was evaluated at the time of clinical presentation, comorbidity, and type of AML. Patients who participated in a clinical trial had a median age of 46 years (range, 16–73 years), whereas those not included were significantly older (median age of 63 years; range, 21–83 years). Survival was significantly better in patients treated in a clinical protocol (median overall survival of 15 months vs. 3.4 months). For survival results in population-based studies, see Table 1. An increase in median survival may possibly, at least partly, be explained by improved supportive care over the past decades.

| Population | Median age, years | Median survival, weeks | Reference |
|------------|------------------|------------------------|-----------|
| Northern Sweden | 63 | 7 | 25 |
| Northern England | 71 | 8 | 89 |
| Italy | 69 | 28 | 20 |

TABLE 2
Selected Risk Factors Associated With Acute Myeloid Leukemia

Genetic disorders
- Down syndrome
- Klinefelter syndrome
- Patau syndrome
- Ataxia telangiectasia
- Shwachman syndrome
- Kostman syndrome
- Neurofibromatosis
- Fanconi anemia
- Li-Fraumeni syndrome

Physical and chemical exposures
- Benzene
- Drugs such as pipobroman
- Pesticides
- Cigarette smoking
- Embalming fluids
- Herbicides

Radiation exposure
- Nontherapeutic, therapeutic radiation

Chemotherapy
- Alkylating agents
- Topoisomerase-II inhibitors
- Anthracyclines
- Taxanes

Etiology
The development of AML has been associated with several risk factors, as summarized in Table 2. Generally, known risk factors account for only a small number of observed cases. These include age, antecedent hematologic disease, and genetic disorders; as well as exposures to viruses as well as radiation, chemical, or other occupational hazards and previous chemotherapy.

Leukemogenesis is a multistep process that requires the susceptibility of a hematopoietic progenitor...
cell to inductive agents at multiple stages. The different subtypes of AML may have distinct causal mechanisms, suggesting a functional link between a particular molecular abnormality or mutation and the causal agent. Most cases of AML arise de novo without objectifiable leukemogenic exposure.

Genetics

Genetic factors

Among children, genetic disorders and constitutional genetic defects are important risk factors associated with AML (Table 1). Children with Down syndrome have a 10-fold to 20-fold increased likelihood of developing acute leukemia. Other inherited diseases associated with AML include Klinefelter syndrome, Li-Fraumeni syndrome, Fanconi anemia, and neurofibromatosis. A recent study found that other risk factors for developing AML in children include race/ethnicity, the father's age at time of conception, and time since the mother's last live birth. Specifically, Asian/Pacific Islander children had a higher risk than non-Hispanic white infants; children born to fathers aged >35 years, compared with those aged 20 to 34 years, also were found to have an increased risk; and a longer time since the last live birth (at least 7 years) resulted in an elevated risk of children developing AML.

In this context, acute promyelocytic leukemia (APL) has been investigated in detail. Representing an example of a unique AML subtype (FAB M3) with a characteristic morphology associated with distinct chromosomal and gene rearrangement aberrations, it has been shown to also have distinct epidemiologic features. For yet unknown reasons, an increased incidence of APL has been recognized in adult patients originating in Latin America and in Southern Europe. Of interest, the APL-specific gene rearrangement is different in Latinos, with the majority of breakpoints in the RARα gene in the PML/RARα transcript in intron 6 (called bcr1). It therefore is speculated that this particular breakpoint site may be determined genetically.

Acquired genetic abnormalities

Acquired (“somatic”) clonal chromosomal abnormalities are found in 50% to 80% of AML cases, with rising incidences in patients with secondary leukemia or older age. Frequently found abnormalities include loss or deletion of chromosome 5, 7, Y, and 9, translocations such as t(8;21)(q22;q22); t(15;17)(q22;q11), trisomy 8 and 21, and other abnormalities involving chromosomes 16, 9, and 11.

Multiple studies have demonstrated the prognostic importance of cytogenetic abnormalities in AML, making this at present the most important predictor of short-term and long-term outcome: Patients with a good prognosis are those with functional inactivation of the core binding factors (CBFs): AML1 and CBFB. These cases include patients with AML and t(8;21)(q22;q22) or inv(16)(p13;q22), 2 of the most frequent recurrent cytogenetic abnormalities in de novo AML in younger patients.

Poor-risk patients have a loss of all or part of chromosome 5 or 7, translocations involving 11q23, or abnormalities of chromosome 3.

A model of a “2-hit-hypothesis” for the AML phenotype by so-called Class 1 and 2 mutations has been suggested. It describes the cooperativity of activating mutations in FLT3 (Fms-like tyrosine kinase 3) (=Class 1) and gene rearrangements involving hematopoietic transcription factors (=Class 2). The expression of both classes may result in the AML phenotype. FLT3 mutations have been associated with all subtypes of AML, and with the majority of known chromosomal translocations associated with AML. In this hypothesis, FLT3 mutations serve as exemplary of Class 1 mutations that, alone, confer a proliferative and survival advantage to hematopoietic progenitors but do not affect cell differentiation. Further examples of Class 1 mutations are activating mutations in N-RAS or K-RAS in AML. In contrast, Class 2 mutations would be exemplified by AML1/ETO, CBFB/SMMHC, PML/RARα, and MLL-related fusion genes. They appear to impair hematopoietic differentiation, but are not sufficient to cause leukemia when expressed alone. This new hypothesis may have important implications for novel treatment approaches (e.g., molecular targeting of both FLT3 and fusion proteins).

Data have been published recently showing that individuals with certain polymorphisms in genes metabolizing carcinogens have an increased risk of developing AML. NAD(P)H:quinone oxidoreductase 1 (NQO1), for example, is a carcinogen-metabolizing enzyme that detoxifies quinones and reduces oxidative stress. A polymorphism at nucleotide 609 of the NQO1 complementary DNA results in a lowering of the enzymes’ activity. This polymorphic variant is associated with a predisposition to therapy-related AML and selected cytogenetic subgroups of de novo AML.

Physical and Chemical Factors

A vast variety of environmental and chemical exposures are assumed to be associated with a variably elevated risk of developing AML in adults. Only a limited number of hazards will be mentioned here.

Exposure to ionizing radiation is linked to AML. Among survivors of the atomic bomb explosions in
Japan, an increased incidence of AML was observed, with a peak at 5 to 7 years after exposure. Also, therapeutic radiation has been found to increase the risk of secondary AML.63

Chemotherapeutic agents, such as alkylating agents and topoisomerase II inhibitors, have been reported to increase the incidence of AML.64,65 A number of other substances (therapeutic66 and occupational11) have been linked to an increased risk of AML. Chronic exposure to certain chemicals clearly shows an increased risk for the development of AML. Benzene is the best studied and most widely used potentially leukemogenic agent.67 Persons exposed to embalming fluids, ethylene oxides, and herbicides also appear to be at increased risk. Furthermore, smoking has been discussed to be associated with an increased risk of developing AML (particularly of FAB subtype M2), especially in those persons aged 60–75.37

Viruses

Viruses, particularly RNA retroviruses, have been found to cause many neoplasms in experimental animals, including leukemia.68 However, to our knowledge, a clear retroviral cause for acute myeloid leukemia in humans has not been identified to date. An association between the exposure to certain viruses and the development of AML has been suggested. Parvovirus B19 exposure could play a role in the pathogenesis of AML.69 To our knowledge, however, it has so far not been demonstrated that simple infection with either an RNA- or DNA-based virus alone is a cause of acute myeloid leukemia.

Secondary AML

For most patients with acute leukemia, the cause of the disease is unknown. “The true secondary AML” has been recommended to refer to patients who have a clinical history of prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents; it is thus a rather broad category.66 Greater than 90% of secondary leukemias are of myeloid origin and have a particularly poor outcome, with a lower incidence of patients achieving a complete remission and a shorter duration of survival than for patients with de novo AML.70–72

Treatment-related secondary leukemia was first observed in survivors of successfully treated Hodgkin disease,73 which extended later to include survivors of ALL74 and other disease entities such as multiple myeloma.75

The development of secondary AML peaks in the 5 to 10 years after therapy. The distinct pattern of cytogenetic and genetic abnormalities in secondary or treatment-related AML is quite remarkable.76 It is a subset of 10% to 20% of patients with AML in whom the disease arises after previous therapy for other malignancies. The risk of therapy-related AML after intensive chemotherapy often is increased 100 times or more.77

Specific cytogenetic abnormalities currently serve as the most important factor in distinguishing differences in AML biology, response to treatment, and prognosis.49 The different abnormalities result in gene rearrangements that may reflect the etiology and pathogenesis of the disease.78 Treatment-related or secondary leukemias are examples in which genetic aberrations provide information regarding its specific etiology. In understanding the mechanisms associated with the development of secondary AML, general facts concerning leukemia etiology can be elucidated.

In this context, genetic pathways with different etiology and biologic characteristics have been proposed for cytogenetic changes that can be related to previous exposure to different chemically well-defined cytostatic agents with a known mechanism of action.79 Among those are alkylating agents: deletions or loss of 7q or monosomy 7 with normal chromosome 5,64,80,81 and deletions or loss of 5q or monosomy 5.82 For epipodophyllotoxins, balanced translocations to chromosome bands 11q23, primarily in children, have been described.74 Topoisomerase II inhibitors have been linked to t(8;21), inv(16).83 Topoisomerase II inhibitors, anthracyclines, and mitoxantrone,84 as well as radiotherapy,85 may be associated with therapy-related acute promyelocytic leukemia with t(15;17) and chimeric rearrangements between PML and RARA genes as well as different translocations to chromosome bands 11q15 and chimeric rearrangement between the NUP98 gene and its partner genes.86 Another subgroup includes 10% to 15% of all patients with secondary AML, with normal karyotype or various chromosome aberrations uncharacteristic of t-AML.79

In the future, many more—as yet unknown genetic and epigenetic changes—may be discovered. To our knowledge to date, methylation of the promoter of p15/IN4b, retinoic acid receptor (RAR)β2, SOCS-1 and epigenetic changes—may be discovered. To our knowledge to date, methylation of the promoter of p15/IN4b, retinoic acid receptor (RAR)β2, SOCS-1 and other genes are frequent abnormalities observed in a high percentage of patients with AML,87 especially in patients with secondary AML.88

The observed changes may pose an option for future attempts to decipher epidemiologic and etiologic findings as well as accelerate the development of new treatment strategies.

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