Acute Myeloid Leukemia: Epidemiology and Etiology

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3.1 Epidemiology

3.1.1 Introduction

Although acute leukemias are infrequent diseases, they are highly malignant neoplasms responsible for a large number of cancer-related deaths. Acute myeloid leukemia (AML) is the most common type of leukemia in adults, yet continues to have the lowest survival rate of all leukemias. While results of treatment have improved steadily in younger adults over the past 20 years, there have been limited changes in survival among individuals of age >60 years [1, 2].

3.1.2 Incidence

It is estimated that 44 240 individuals in the USA will be diagnosed with one form of leukemia. Approximately 21 790 will die of their disease [6]. Although the incidence of acute leukemias accounts for less than 3% of all cancers, these diseases constitute the leading cause of death due to cancer in children and persons younger than 39 years of age [3–5].

AML accounts for approximately 25% of all leukemias in adults in the West and constitutes the most frequent form of leukemia [3, 6]. Worldwide, the incidence of AML is highest in the USA, Australia, and Western Europe. The age-adjusted incidence rate of AML in the USA is approximately 3.7 per 100 000 persons (= 2.6 per 100 000 when age-adjusted to the world standard population) [6]. In the USA, 13 410 men and women (7060 men and 6350 women) are estimated to be newly diagnosed with AML in 2007 [6]. Figure 3.1 shows age-standardized incidence rates stratified by various countries [7].

3.1.3 Age

Leukemia is the most common cancer diagnosis in children who are younger than 15 years, with an overall incidence of 4.3/100 000 in the USA [8]. In this age group, however, acute lymphocytic leukemia (ALL) is about five times more common than AML, thus accounting
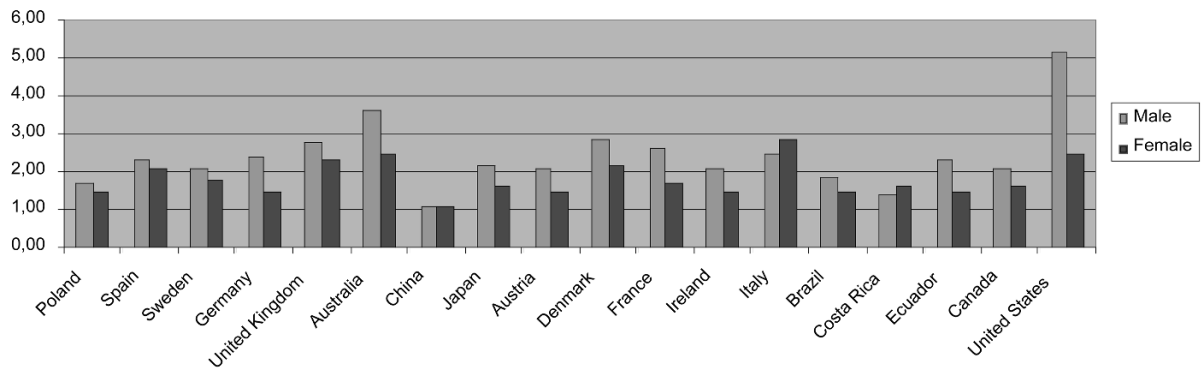
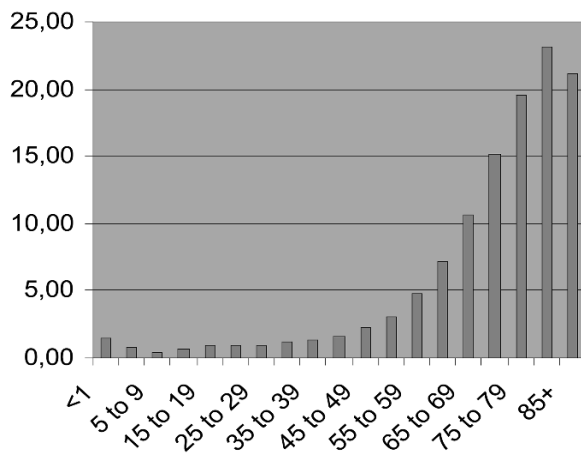**Fig. 3.1.** Age-standardized world incidence rates of AML 1997 [92].

Fig. 3.2. Age-specific incidence of AML: USA 2000–2004 [6].

for about 76% of all childhood leukemia diagnoses. Conversely, AML makes up only 15–20% of cases in those aged 15 years or younger [9]. The peak incidence rate occurs in the first year of life and then decreases steadily up to the age of 4 years. The incidence rate remains relatively constant in childhood and early adulthood [10].

AML is thus a disease of older adults (see Fig. 3.2). The distribution of prevalent cases of all leukemias in the UK shows that 42.8% of patients are above the age of 65 years [11]. Patients newly diagnosed with AML have a median age of 65 years [12]. It is rare before the age of 40; thereafter the incidence increases progressively with age.

From 2000–2004, the US incidence rate in people under the age of 65 was only 1.7 per 100 000, while the incidence rate in people aged 65 or over was 16.8 per 100 000 (Fig. 3.2) [6]. Therefore, of the estimated 13 400 new AML diagnoses in the US, over half will affect patients 60 years of age or older, a population considered "elderly" in leukemia literature.

The high incidence and poor prognosis of AML in the elderly is suspected to be based on the frequent progression of myelodysplastic syndromes (MDS) to AML, an increased incidence of MDS with age appears to explain both. The common AML subtype in the elderly shares characteristics with AML that follows MDS, Fanconi's anemia, alkylating agent chemotherapy (see also Sect. "Etiology" below), and an estimated 10–15% 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 the residual hematopoietic precursor cells. A higher frequency of unfavorable biologic and prognostic factors, rather than age per se, is thus the major determinant for the inferior prognosis for elderly patients. By contrast, AML with genotypes typical of younger patients, which may be considered as true de novo AML, has an approximately constant incidence throughout lifetime, also in progressive age groups. Five percent of elderly patients with AML are estimated to belong to the true de novo AML-group, which shows consistency with the incidence in younger patients [13].

Although incidence rates for AML have been near stable over time among the different age groups, there is a slight increase among the oldest group [14].

3.1.4 Gender and Ethnicity

The incidence of AML varies to a certain degree with gender and race. In the SEER data base for children aged 1–4 years there is an incidence rate of 0.9 per 100 000 for boys and 0.8 for girls [6]. In the first few years of life, the incidence of AML in whites is three-fold higher than in blacks; however, blacks have slightly higher rates of AML among children 3 years of age and older [16].

In most countries a slight male predominance of AML in adults has been documented. In 2004, the US age-adjusted incidence rate of AML was 3.6 per 100 000 for both sexes, 4.5 per 100 000 for males, and 3.0 per 100 000 for females [6]. The incidence rate of US males is substantially higher than the incidence rates of males in all other countries (Fig. 3.1).

In the USA between 2000 and 2004, AML was more common in whites (3.7 per 100 000) than in blacks (3.2 per 100 000).

3.1.5 Mortality

Untreated AML is a fatal disease. Although it is possible to support patients for a certain period (median survival: 11–20 weeks) [16, 17], patients not receiving specific treatment ultimately succumb to the leading complications associated with bone marrow failure, such as infection and hemorrhage. Patients typically seek medical attention for symptoms related to infection or bleeding. These patients require immediate therapeutic intervention. Some patients are not candidates for cytotoxic therapy, 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 [18]. Firm stratification criteria for decision-making in this setting are not uniformly established and patient- and disease-specific risk assessment has become an additional area of investigation [19].

After long-term increases or mostly level trends that date from the 1930s, death rates for all leukemias were decreasing in the 1990s in the USA and Europe [20, 21]. In 2000–2004, the US age-adjusted mortality rate of AML was 2.7 per 100 000. As is the case with incidence, the mortality associated with AML varies with age, gender, and race. Mortality rates in the USA increase with age. Between 1996 and 2000, the age-adjusted mortality rate showed its peak at 17.6 per 100 000 in people aged 80–84.

The mortality rate for males is higher than that for females, with the US age-adjusted mortality rate at 3.5 per 100 000 for males and 2.2 per 100 000 for females in (2000–2004). AML mortality has for several years been greater in whites than in blacks. The US age-adjusted mortality rate was 2.8 per 100 000 for whites and 2.2 per 100 000 for blacks in the years 2000–2004 [6]. It is estimated that 7800 adults will have died of AML in 2003 in the USA [12, 22].

3.1.6 Survivorship I

A comprehensive report on the total leukemia incidence and survival in the USA covered the period 1973–1990 [23]. Overall survival rates for all leukemia (including chronic leukemia) patients improved only slightly when comparing the periods 1974–1976 and 1983–1989, but were consistently higher in whites compared with blacks, with little gender difference. When analyzing survival rates in more detail, it was found that in comparing the period 1974–1983 with 1984–1993, overall survival rates improved steadily among all races/age groups younger than the age of 45 years. However, for blacks 45 years or older, there was little improvement in overall survival. In particular, for blacks older than 65 years, survival rates for leukemia were decreasing, which was not observed in earlier data [14]. The reasons for these gender and racial differences seen in leukemia (including all subtypes) remain unclear.

The overall US survival rate associated with AML from 1992–1998 was approximately 20% [22].

Figures 3.3–3.5 depict 5-year survival rates stratified by age, gender, and race. 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 relative survival rate than whites (20.8 vs. 18.2%) in several areas of the United States [6].

Survival rates have increased in the last decade among younger groups (from 9% in the 1980s to 35% in the 1990s), but have not changed in the older group. Research now focuses increasingly on improving outcome in the patient group mainly affected by the disease.

In a large Italian population-based study (n = 1005), median survival of patients aged > 60 years with AML either treated with supportive or aggressive therapy was 5 and 7 months, respectively. In patients > 70 years,
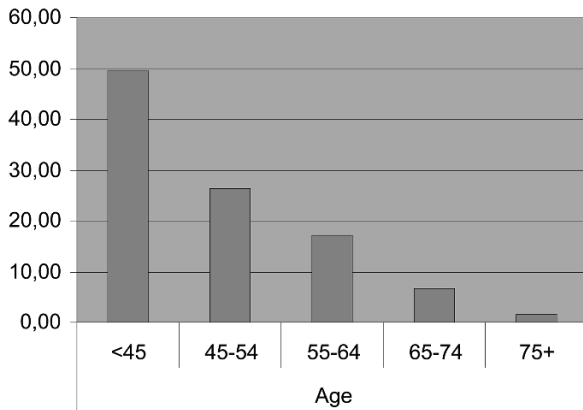
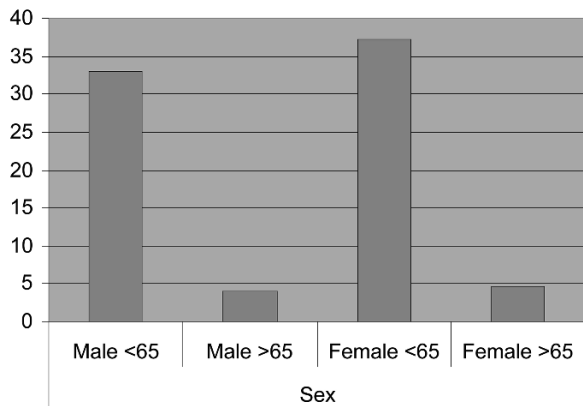**Fig. 3.3.** Age associated with 5-year relative survival: USA 1996–2003 [6].

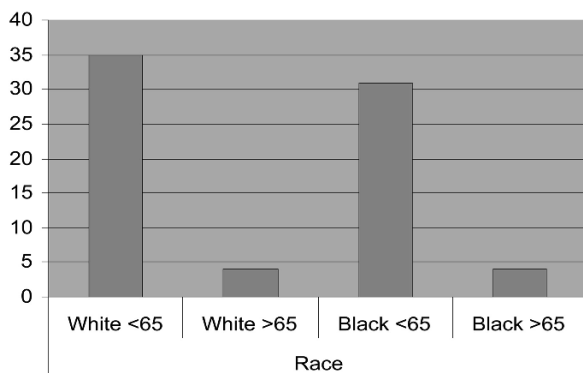**Fig. 3.4.** Sex associated with 5-year relative survival: USA 1996–2003 [6].

Fig. 3.5. Race associated with 5-year relative survival: USA 1996–2003 [6].

median survival was 4 months and this, notably, was regardless of the type of therapeutic effort [18]. Age has further been shown to be inversely associated with (1) referral to a treatment center [24], and/or inclusion into a clinical trial [25], (2) tolerance to induction treatment (early death or death during the immediate postchemotherapy phase) [26], and (3) the ability to achieve remission [27, 28]. In older patients (>60 years), standard induction therapy achieves complete remission in only 30–50% of treated individuals [29].

Even though results of major clinical studies report higher rates of disease-free survival (e.g., 4-year survival rates of up to 42%) [30], data can differ considerably. The differences in survival results seen among various trials using similar chemotherapy may be explained by the prevalence of negative prognostic characteristics within a study population [31]. 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 on age distribution, treatment decisions, remission rates, and survival in AML do show quite significant variability to some of the large clinical investigations. In one report, of a total of 170 AML patients, 55% were treated outside a study protocol. Non-study patients differed significantly from patients included in clinical trials with respect to age and performance status at clinical presentation, comorbidity, and type of AML. Patients who participated in a clinical trial had a median age of 46 years (16–73 years), whereas those not included were significantly older (median age 63 years; 21–83 years). Survival was significantly better in patients treated in a clinical protocol (median OS: 15 vs. 3.4 months) [25]. For survival results in population-based studies see Table 3.1. It can be assumed that

Table 3.1. Selected population-based studies of myeloid neoplasias in various populations: survival irrespective of treatment strategy [94]

Population	Median age	Median survival (weeks)
Northern Sweden (24)	63	7
Northern England (93)	71	8
Italy (18)	69	28

part of the increase in median survival in the last years may be attributed to improved supportive care over past decades.

3.1.7 Survivorship II

At St. Jude Children's Hospital, the incidence of and risk factors for the development of late sequelae of treatment in patients who survived for more than 10 years (median: 15 years) after diagnosis of childhood AML have been evaluated. The most common late effects in adulthood consisted in growth abnormalities (51%). Depending on the treatment modality (chemotherapy only; combined chemo-, radiotherapy; or combined chemo-, radiotherapy with consecutive bone marrow or peripheral stem cell transplantation), endocrine abnormalities, cataracts, cardiac abnormalities, academic difficulties, and secondary malignancies resulted in 14–51%. Besides physical late effects, psychosocial complications were observed in long-term survivors [32].

Patients that survived AML and treatment have also been monitored in a long-term follow-up at the University of Texas M.D. Anderson Cancer Center [33]. Some very relevant conclusions have been drawn in this report: Only 10% of all 1892 patients entered the potentially cured cohort, which was defined as the patient population in complete remission after a follow-up of 3 years. Those patients in the potentially cured cohort were most likely to be able to return to work, suggesting that the major threat to patients with newly diagnosed AML is the disease and not the treatment.

3.2 Etiology

The development of AML has been associated with several risk factors. Remarkably though, as of yet defined risk factors account for only a small number of observed cases [34]. These include age, antecedent hematological disease, genetic disorders as well as exposures to viruses, radiation, chemical or other occupational hazards, and previous chemotherapy [9, 35–37] (see Table 3.2).

The development of leukemia is a process consisting of multiple single steps that requires the susceptibility of a hematopoietic progenitor cell to inductive agents at multiple stages. The different subtypes of AML may have distinct mechanisms, suggesting a functional link

Table 3.2. Selected risk factors associated with AML

Genetic disorders	Down syndrome
	Klinefelter's syndrome
	Patau's syndrome
	Ataxia telangiectasia
	Schwachman syndrome
	Kostman syndrome
	Neurofibromatosis
	Fanconi anemia
	Li-Fraumeni syndrome
Physical and chemical exposures	Benzene
	Drugs as Pipobroman
	Pesticides
	Cigarette smoking Embalming fluids
	Herbicides
	Drugs as Pipobroman
Chemotherapy	Alkylating agents Topoisomerase II inhibitors
	Anthracyclines
Radiation exposure	Nontherapeutic, therapeutic radiation

between a particular molecular abnormality or mutation and the causal agent [38]. In most cases of AML the malignancy arises de novo and no leukemogenic exposure can be deciphered.

3.2.1 Genetics

3.2.1.1 Genetic Factors

Genetic disorders and constitutional genetic defects are important risk factors associated with AML in children [37]. Children with Down syndrome have a 10- to 20-fold increased likelihood of developing acute leukemia [39, 40]. Other inherited diseases associated with AML include Klinefelter's syndrome, Li-Fraumeni syndrome [41], Fanconi anemia, and neurofibromatosis [9]. Furthermore, risk factors for developing AML in children were identified and include race/ethnicity, the father's age at time of conception, and time since the mother's last live birth [35]. Specifically, Asian/Pacific

Islander children had a higher risk than non-Hispanic white infants; children born to fathers older than 35, compared to those aged 20–34, had an increased risk; and longer time since the last live birth (at least 7 years) resulted in an increased risk.

In this context, acute promyelocytic leukemia (APL) has been investigated in more 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 separate epidemiological features. For yet unknown reasons, an increased incidence of APL has been recognized in adult patients originating in Latin America and in children in Southern Europe. Of interest, the APL-specific gene rearrangement is different in patients of Latin American decent, with the majority of breakpoints in the RARα gene in the PML/RARα transcript in intron 6 (called bcr 1). It is therefore speculated that this particular breakpoint site may be determined genetically [42–45].

3.2.1.2 Acquired Genetic Abnormalities

Acquired ("somatic") clonal chromosomal abnormalities are found in 50–80% of AML [24, 46–49] with rising incidences in patients with secondary leukemia [50] or older age [13, 51, 52]. 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.

Cytogenetic abnormalities constitute at present the most important predictors of short- [53–55] and long-term [33] outcome. To name selected examples, patients with a good prognosis are those with functional inactivation of the core binding factors (CBFs): AML1 and CBFβ. These cases include patients with AML and t(8;21) (q22;q22) or inv(16) (p13;q22), two of the most frequent recurrent cytogenetic abnormalities in de novo AML in younger patients [56].

Poor-risk cytogenetics have a loss of all or part of chromosome 5 or 7, translocations involving 11q23, or abnormalities of chromosome 3 [57].

A model of a "two-hit-hypothesis" for the AML phenotype by so-called class I and II mutations has been established. It describes the cooperativity of activating mutations in FLT3 (Fms-like tyrosine kinase 3) (= class I) and gene rearrangements involving hematopoietic

transcription factors (= class II). The expression of both classes may result in the AML phenotype. FLT3 mutations can appear in 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 I mutations that, alone, confer a proliferative and survival advantage to hematopoietic progenitors but do not affect cell differentiation. Further examples of class I mutations are activating mutations in N-RAS or K-RAS in AML. In contrast, class II mutations would be exemplified by AML1/ETO, CBFβ/ SMMHC, PML/RARα, and MLL-related fusion genes. They appear to impair hematopoietic differentiation, but are not solely sufficient to cause leukemia. This new hypothesis may have important implications to novel treatment approaches (e.g., molecular targeting of both, FLT-3 and fusion proteins) [58].

Data has been published showing that individuals with certain polymorphisms in genes metabolizing carcinogens have an increased risk of developing AML [59]. 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 [60] and selected cytogenetic subgroups of de novo AML [61].

3.2.2 Physical and Chemical Factors

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

Exposure to ionizing radiation is linked to AML [62]. Among survivors of the atomic bomb explosions in Japan, an increased incidence of AML was observed with a peak at 5–7 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] and will be discussed in detail below. A number of other substances (therapeutic [66] and occupational [9]) 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 widely used potentially leukemogenic agent [67]. Persons exposed to embalming fluids, ethylene oxides, and herbicides also appear to be at increased risk [68]. Furthermore, smoking has been discussed to be associated with an increased risk of developing AML (particularly of FAB subtype M2), especially in those aged 60–75 [69]. For summary see Table 3.2.

3.2.3 Viruses

Viruses – particularly RNA retroviruses – have been found to cause many neoplasms in experimental animal models, including leukemia [70]. As of now, a clear retroviral cause for AML in humans has not been identified even though an association between the exposure to certain viruses and the development of AML has been suggested. Parvovirus B19 could thus play a role in the pathogenesis of AML [71]. It has so far not been demonstrated, however, that simple infection with either a RNA- or DNA-based virus alone is a cause of AML.

3.2.4 Secondary AML

As mentioned, the cause of the disease is unknown for most patients with acute myeloid leukemia. "The true secondary AML" has been recommended to be referred to patients who have a clear clinical history of prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents; it is thus a rather broad category [56]. Secondary leukemias are in more than 90% of myeloid origin. Patients have a particularly poor outcome, with a lower incidence of achieving complete remission and shorter duration of survival than for patients with de novo AML [72–74].

Treatment-related secondary leukemia was first observed in survivors of successfully treated Hodgkin's disease [75]. Later on, survivors of ALL [76] and other disease entities such as ovarian or breast cancer and multiple myeloma [77] were included. The development of secondary AML shows a maximum in the 5–10 years following therapy. The distinct pattern of cytogenetic and genetic abnormalities in secondary or treatment-related AML is worthy of notice [78]. AML arises after previous therapy for other malignancies in a subset of 10–20% of patients. The risk of therapy-related AML

after intensive chemotherapy may be increased to more than 100 times [79].

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 [80]. Treatment-related or secondary leukemias are examples in which genetic aberrations provide information on its specific etiology. In understanding the mechanisms associated with the development of secondary AML, general facts about the possible etiology of leukemia can been 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 [81]. Among those are for alkylating agents: deletions or loss of 7q or monosomy 7 with normal chromosome 5 [82–84], and deletions or loss of 5q or monosomy 5 [85]. For epipodophyllotoxins, balanced translocations to chromosome bands 11q23, primarily in children, have been described [76]. Topoisomerase II inhibitors have been linked to t(8;21), inv(16) [86]. Topoisomerase II inhibitors, anthracyclines, mitoxantrone [87], as well as radiotherapy [88] may be associated with therapy-related acute prolymphocytic 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 [89].

Another subgroup includes 10–15% of all patients with secondary AML, with normal karyotype or various chromosome aberrations uncharacteristic of t-AML or at least not identified as such as of now [90].

It is to be expected that in the future, many more genetic and epigenetic changes may be discovered. As of now, methylation of the p15 promoter is the only abnormality observed in a high percentage of patients with AML, especially in patients with secondary AML [91].

In current times there is a rapid gain in insight regarding epi-/genetic changes associated with the development of hematological malignancies like AML. It can be hoped for that many epidemiological and etiological findings may be explained and the development of new specific treatment strategies can further be enhanced on this basis.

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