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Series Editors: Dominik Schneider · Dirk Reinhardt

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Acute Myeloid Leukemia in Children

Standard of Care and Future Perspectives

Springer

Pediatric Oncology

Series Editors

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This series provides up-to-date information on important topics in pediatric oncology, from the diagnosis and treatment of particular forms of disease through to, for example, radiation oncology, supportive care, and survivorship. The entire spectrum of clinical management is covered with the aim of equipping readers with the latest knowledge relevant to daily practice. In addition, clinical, methodological, and research issues are addressed. The series benefits from homogeneous design and consistently high quality of illustrations. The volume editors are internationally renowned authorities and contributing authors have been selected for their expertise in the subjects discussed. *Pediatric Oncology* will serve pediatric oncologists, fellows, and residents both as a comprehensive source of information and as a quick reference. The series will also be of interest to pediatricians and general practitioners.

Daisuke Tomizawa • Edward Anders Kolb
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Editors

Acute Myeloid Leukemia in Children

Standard of Care and Future Perspectives

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Preface

On behalf of all the authors, we are very pleased to publish the first edition of *Acute Myeloid Leukemia in Children: Standard of Care and Future Perspectives* in the *Pediatric Oncology* book series. Acute myeloid leukemia (AML) is the second most common type of leukemia during childhood. Progress in diagnosis and treatment over a half century based on national and international collaborative efforts on both basic and clinical research resulted in a true success story now reaching approximately 70–80% overall survival rate in children with this disease.

This book consists of 19 chapters written by prominent international experts in this field, which describes up-to-date information on key topics and issues in pediatric AML, including the epidemiology, biology, diagnosis and treatment of particular forms of the disease, supportive care, and survivorship.

We would like to acknowledge Ms. Madona Samuel of Springer for her enormous assistance to publish this book. We dedicate this book to all patients and their families, as well as clinicians, researchers, nurses, and other health care workers involved in pediatric AML. We truly wish this book to be useful not only for pediatric hematologist/oncologists but also for fellows, residents, general practitioners, and experts of other fields including adult hematologists both as a comprehensive source of information and as a quick reference.

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Part I

Epidemiology and Biology of Pediatric AML

Overview and Epidemiology of Pediatric AML

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D. Spencer Mangum and Edward Anders Kolb

1.1 Acute Myeloid Leukemia (AML) Classification History

In the mid-1800s, reports of a disease characterized by excessive white blood cells began to emerge, which in 1847 was named "leukemia" by pathologist Rudolph Virchow. By 1900, white blood cells could be classified as either myeloid or lymphoid based on work by Otto Nageli. By 1913, leukemia could be categorized according to the chronicity and the hematopoietic lineage of the disease, namely: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [1].

1.1.1 French, American, British (FAB) Classification System

In 1976, a group of seven French, American, and British hematologists published a classification system for the acute leukemias now known as the FAB classification system. AML was subdivided into six different subcategories (M1–M6) based on the morphology of the blast cells, which reflected both the stage of cellular maturation and the type of myeloid lineage of the leukemia. M1, M2, and M3 AML consisted of primarily granulocytic lineages arrested at different maturation stages (with M3 being distinctly arrested at the promyelocyte stage), M4 AML contained a mixture of granulocytes and monocytes, M5 AML was predominantly monocytes, and M6 represented AML from an erythroid lineage [2]. In 1985, M7 (megakaryoblastic AML, AMKL) and M4 with eosinophilia (M4eo) were added to the FAB classification system [3, 4]. It was not until 1991 that M0 was recognized in the FAB classification system as a result of both its rarity and very early maturational arrest with only minimal myeloid differentiation [5]. While the FAB system was a useful framework for the classification of AML, with further discovery of the different somatic genetic alterations that drive AML and a greater understanding of the contexts in which AML can develop, a more expansive classification system was needed.

1.1.2 World Health Organization (WHO) Classification System

In the 1960s, the World Health Organization (WHO) began to organize and classify tumors of

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all types, which are published in what have become colloquially known as "blue books." In 2001, the WHO published its first hematopoietic specific tumor classification system based on the input of more than 100 worldwide experts, which was subsequently updated in 2008, again in 2016, with a newest edition planned for publication in 2022 [6–8]. In contrast to the FAB system that focused on cellular morphology, the WHO classifies AML first by the presence or absence of recurrent genetic abnormalities (which has implications for both treatment and prognosis), and additionally recognized the significance of: myelodysplasia related AML (AML-MR) in which AML either arose from an antecedent myelodysplastic syndrome (MDS) or has MDS-like features, AML/myeloid neoplasms occurring in the setting of Down Syndrome (DS), extramedullary AML, as well as secondary myeloid neoplasms that in the newest guidelines will encompass both therapy-related AML (t-AML) and AML arising from germline mutations [9]. Only in the absence of recurrent genetic abnormalities and the situations listed above, does the WHO recommend classifying AML using a morphologic-based system as created by the FAB group. (See Chap. 4 regarding diagnosis and WHO classification for further details.)

1.2 AML: Age and Recurrent Genetic Abnormalities

AML has both the highest incidence and mortality in the United States among all the leukemias [10]. However, the majority of AML occurs in adults. Aside from a short dip after infancy, the incidence of AML continually increases with age [11], with a median age at diagnosis of 68 [10], and almost 90% of cases occurring in patients over 65 years of age (annual incidence rate per 100,000 people by age group in 2019: <15 years = 0.7; 15–39 = 1.2; 40–64 = 3.6; 65–74 = 14; ≥75 = 25.2) [12] (Fig. 1.1). Within the pediatric age range, the peak incidence of AML occurs within infants less than 1 year of age (with 14.7 cases per one million person years), which after decreasing through early childhood (low of 4.6 cases per one million person years during ages 5–9), begins to increase again after the age of 10 reaching up to 8.7 cases per one million person years by the ages of 15–19 [16, 17].

While only a small minority of AML cases are in pediatric patients, AML accounts for 18% of acute leukemias occurring in children [16, 17], which is notable as leukemia is the most common cancer in childhood accounting for nearly one in three childhood cancer cases [16]. When contrasting the two most common childhood leukemias, ALL and AML, the incidence of each is roughly a 1:1 ratio through the first year of life, 7:1 ratio from ages 1–10 (which corresponds to the time in which ALL has its highest incidence), and then occurs at a 3:1 ratio in adolescents aged 15–19 years of age [18, 19].

Within AML, age is not just a number. Genetic profiling of pediatric versus adult AML patients identifies significantly different drivers of disease [13, 15], with younger patients having relatively much higher survival [11, 20], demonstrating that pediatric versus adult AML are distinct entities within the same spectrum of myeloid malignancies.

1.2.1 Chromosomal Structural Rearrangements

In pediatric AML, chromosomal structural rearrangements are a common defining feature and generally correlate with specific FAB groups. The translocation t(8;21) (*RUNX1::RUNX1T1*) accounts for approximately 15% of pediatric AML and is more commonly M2 AML. The translocation t(15;17) (*PML::RARA*) accounts for approximately 5% of pediatric AML and represents almost all of M3. Inversion of chromosome 16, inv(16)/t(16;16), creates a *CBFB::MYH11* fusion that accounts for 10–15% of pediatric AML and corresponds with M4eo AML. And lastly, *KMT2A* rearrangements account for 10–15% of pediatric AML, and most commonly are M4 and M5 AML [14, 21–23].

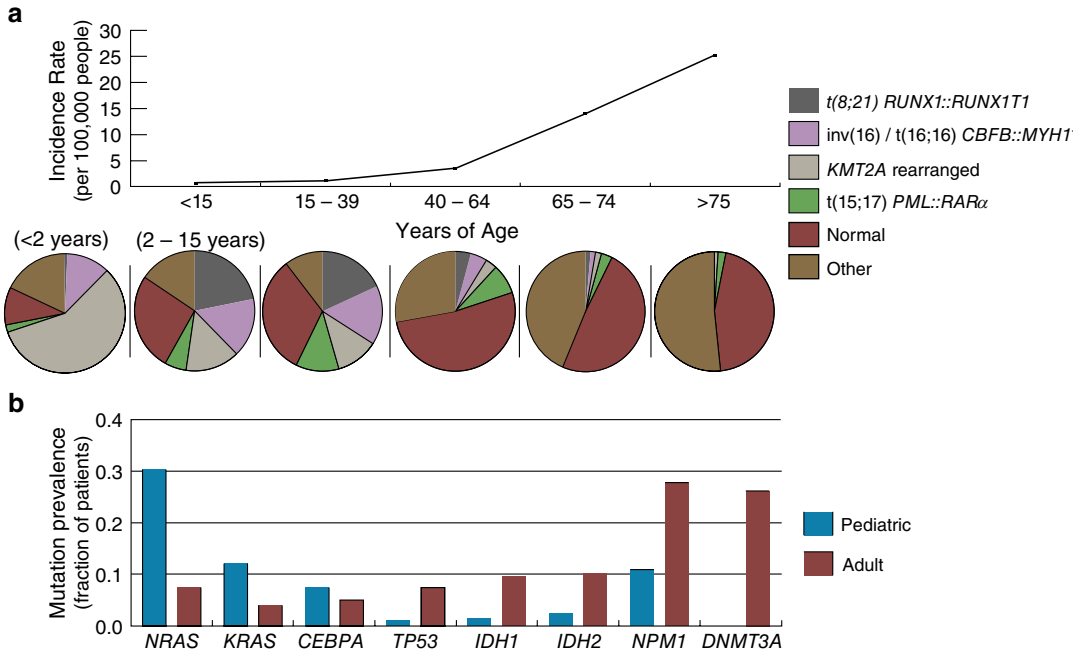

Fig. 1.1 The genetic landscape of pediatric versus adult AML. (**a**) AML incidence and chromosomal structural rearrangements by age. AML is predominantly a disease of the elderly. In childhood, the highest incidence is in infants, which after decreasing through early childhood begins to increase again after the age of ten with thereafter the incidence continually rising throughout life. However, pediatric and adult AML are genetically distinct. AML defining translocations predominate the cytogenetic landscape of pediatric AML. The incidence of such translocations becomes increasingly rare in older patients who are far more likely to have either a normal or complex karyotype (with chromosomal deletions or gains). (Figure adapted from data from SEER [12], Creutzig et al. [13], and Conneely et al. [14]. Not shown are *NUP98* fusions, which have an approximate peak incidence of 5% in pediatric AML, but then which incidence further decreases with age.) (**b**) Somatic gene mutations in pediatric versus adult AML. Beyond structural rearrangements, there are significant differences between pediatric and adult AML in the type and frequency of somatic gene mutations, including single nucleotide variants (SNVs) and small insertions and deletions (INDELS). Whereas *RAS* pathway mutations predominate in childhood, adults have increased rates of *TP53*, *IDH1*, *IDH2*, *NPM1*, and *DNMT3A* mutations. (Figure adapted from Bolouri et al. [15])

AMLs with a t(8;21) or inv(16) are referred to as core binding factor (CBF) AMLs, which portend a better prognosis. CBF is a transcription factor that regulates hematopoiesis, and has both an alpha and beta subunit encoded for by different genes. *RUNX1* is one of the alpha CBF subunits and its normal function is disrupted by the t(8;21) translocation. *CBFB* is the beta subunit and its normal function is disrupted by inv(16) [24]. The t(15;17) translocation leads to a fusion involving a retinoic acid receptor alpha gene (*RARA*), which results in a block of differentiation at the promyelocytic stage (and hence is known as acute promyelocytic leukemia, APL). Treatment with the vitamin A derivative: all trans-retinoic acid (ATRA) forces differentiation of APL blasts and is a highly effective treatment whose effect is enhanced with the addition of arsenic trioxide (ATO) [25]. The gene *KMT2A* is located on chromosome 11, band q23 (11q23) and was formerly known as the *MLL* (mixed lineage leukemia) gene. *KMT2A* translocations can occur at multiple different breakpoints with numerous different partner genes and drive a range of multiple different leukemias across both lymphoid and myeloid lineages. *KMT2A* rearrangements have a particularly high incidence in infants with either AML or ALL, in acute leuke-

mia of ambiguous lineage, as well as in therapy-related AML secondary to topoisomerase inhibitors [26]. In pediatric AML, the effect of *KMT2A* rearrangements on prognosis is dependent on the partner gene [27].

The frequency of these rearrangements changes with the age of the patient, with structural rearrangements predominating in the pediatric age range, but then decreasing in incidence afterward (Fig. 1.1). The t(8;21) (*RUNX1::RUNX1T1*) translocation is almost absent in infancy, but peaks in childhood, adolescents, and young adults, before trailing off in adults and the elderly. The inv(16) *CBFB::MYH11* fusion maintains a more steady incidence throughout life but also has its peak in childhood ages before declining with age [13–15]. The APL t(15;17) translocation occurs throughout life, but peaks in the adolescent and young adult (AYA) ages with a median age of diagnosis of 42 years, after which incidence declines with further aging [13, 28]. *KMT2A* rearrangements account for 35–60% of infantile AML, following which they decline to an approximate 10% incidence through adult life [13, 14]. Once over 80 years of age, the incidence of any of these structural rearrangements becomes almost negligible [13].

More recently identified, patients with translocations involving the gene *NUP98* located on chromosome 11p15 have been described as a less-common (approximate 5% incidence in pediatric AML), but high-risk group with poor outcomes. Similar to *KMT2A*, *NUP98* has multiple different translocation partners, but most commonly partners with *NSD1*, t(5;11) (q35;p15.5) [29]. Also similar to other structural rearrangements, the peak incidence of *NUP98* fusions is in childhood, which then decreases with age [30]. Numerous other rare translocations/fusions have been discovered in the recent decades, but will be addressed in later chapters.

1.2.2 Somatic Gene Mutations

Beyond structural rearrangements, there are also important differences between pediatric and adult AML in the pattern of somatic single gene mutations, including single nucleotide variants (SNVs) and small insertions and deletions (INDELS). Some of the most commonly mutated/altered genes in pediatric AML patients include *RAS* pathway genes (most commonly *NRAS, KRAS,* and *PTPN11*; 30–50% of patients), *FLT3 (*over 20%), *KIT* (over 10%), *WT1 (*over 10%), *NPM1* (10–20%), and *CEBPA* (5–10%) [13–15]. Adults have significantly less *RAS* and *WT1* mutations, whereas they have significantly more frequent *NPM1* mutations (almost 30%). Adults also had relatively more frequent *TP53*, *IDH1*, and *IDH2* mutations (approximately 10% for each), which are rare in children (1–2% incidence for each) [31]. Most frequently, adults harbor *DNMT3A* mutations (approximately 30%), which are very rare in pediatric patients (<1%) [13, 15, 32]. While both adult and pediatric AMLs have relatively low mutational burdens compared to many other adult cancers, the overall mutational burden does increase with age [15].

Activating *FLT3* alterations, either through internal tandem duplication (ITD) or mutations, are associated with worse prognosis and have attracted significant interest in pediatric AML as it is a targetable lesion for treatment [33]. While rare in pediatric AML, *IDH1* and *IDH2* have also garnered interest as they are also targetable lesions for treatment [34]. Currently, *RAS* pathway, *KIT*, and *WT1* mutations are not used for risk stratification [35–37], whereas *NPM1* and *CEBPA* mutations are associated with a more favorable prognosis [36]. However, in cases with overlapping genetic alterations (with specific genetic lesions often being more likely to cluster with other specific genetic lesions), the effect on outcomes can be more complex [15, 36].

1.2.3 Age Influences the Transformative Ability of Genetic Lesions

These differences in genetic drivers between children and adults are not by chance. Hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) undergo changes in their gene expression pattern with age, and

these progenitor cell transcriptome and epigenomic changes affect their susceptibility to transformation by the aforementioned genetic drivers of AML. Known pediatric AML drivers are more transforming in neonatal HSCs and HPCs, and known adult drivers are more transforming in adult HSCs and HPCs [38, 39]. Moreover, consistent with a continually rising incidence of myeloid malignancies through life, accumulation of somatic AML predisposing mutations is common in adults. One study found that among 20 healthy adults aged 50–70, 95% had low-level clonal hematopoiesis with an AML-associated mutation (predominantly *DNMT3A* and *TET2*) [40], whereas clonal hematopoiesis and such mutations are quite rare in healthy children [41].

1.3 AML Non-Genetically Defined Subtypes

Beyond AML with recurrent genetic abnormalities, the context in which AML develops can also have significant importance. WHO guidelines recognize the following as distinct entities of AML:

1.3.1 Myelodysplasia Related AML (AML-MR)

Like AML, myelodysplastic syndrome (MDS) is a clonal hematopoietic disorder of myeloid cells. Unlike AML, it is a relatively indolent neoplasm. MDS is typically characterized by peripheral cytopenias and carries the potential risk of progression to acute myeloid leukemia. In children, MDS is quite rare with an incidence of one to four cases per million and most often occurs in the setting of an inherited bone marrow failure syndrome or from a germline predisposition (such as *GATA2*, *ETV6*, and *SAMD9/SAMD9-L*) [42]. Myelodysplasia related AML (AML-MR) refers to both AML that is the result of evolution of an antecedent MDS, or de novo AML that has MDS-like features. AMLs with myelodysplastic cytogenetic changes, such as monosomy 5, del(5q), and monosomy 7 [43], are uncommon in pediatrics and adults, but then have a particular increase in the elderly as the incidence of myelodysplasia related AML increases with age [14, 29, 44]. The definitive treatment for MDS is hematopoietic stem cell transplant (HSCT) [45]. Similarly, AML with MDS cytogenetic changes is a high-risk form of AML that should be treated with HSCT after obtaining a remission with chemotherapy.

1.3.2 Myeloid Proliferations Related to Down Syndrome

Children with Down Syndrome (DS) are uniquely predisposed to develop a megakaryoblastic proliferation known as transient abnormal myelopoesis (TAM) and leukemia. TAM is a myeloproliferative disorder that occurs in infants with trisomy 21, although the patient may or may not have DS if they have a mosaic form of trisomy 21 that in some cases can be isolated entirely to the hematopoietic system [46]. In utero, among hematopoetic cells with an additional copy of the 21st chromosome, the secondary acquisition of a somatic mutation in *GATA1* leads to impaired megakaryocytic differentiation and proliferation that clinically resembles megakaryoblastic AML (AMKL) [47]. TAM is typically recognizable around birth, and this proliferation is a transient process that typically self-resolves by approximately 3 months of age. TAM only requires treatment with a short course of low-dose cytarabine if the patient is overtly ill as a result of the disease. However, up to 20% of infants die from complications of TAM, which is most often the result of TAM blast invasion of the liver leading to fibrosis and hepatic failure [48]. Depending on the screening practice and criteria used, 10–30% of children with DS can be diagnosed with TAM [49].

In 20–30% of TAM patients, the original TAM clone will evolve into AML, which is referred to as myeloid leukemia associated with Down Syndrome (ML-DS). This transformation is hypothesized to occur secondary to the TAM clone acquiring further transforming genetic

lesions [50, 51]. During this transformation there is a relatively high rate of an initial myelodysplastic phase, which in contrast is rare in non-DS pediatric patients. In further contrast to non-DS MDS that requires HSCT for treatment, DS-related myelodysplasia falls under the ML-DS umbrella and is treated on the same protocols, with the same chemotherapy, and achieves the same outcomes as overt DS-related AML. In fact, approximately 30% of patients treated on the children's oncology group ML-DS study AAML0431 had MDS rather than AML [52, 53]. Most commonly the AML that develops in DS patients is AMKL, although AML with erythroid or even undetermined differentiation also occurs [54]. If this malignant transformation occurs, it generally will occur before the age of four [55, 56]. Altogether, approximately 3% of children with DS develop leukemia, with AML predominating up to age two, with ALL becoming more common thereafter [56].

Due to a combination of exquisite chemosensitivity in ML-DS (resulting in excellent cure rates with an event-free survival of approximately 90%), and a significant susceptibility for complications with chemotherapy in DS patients, ML-DS patients are treated on separate protocols than other AML patients [52]. Sadly, patients with relapsed or refractory ML-DS rarely survive [57, 58]. Note, children without DS develop AMKL as well; however, the genomic landscape in non-DS AMKL is significantly different from ML-DS and is characterized by unique fusions that are rarely found elsewhere. In non-DS AMKL, outcomes are strongly correlated with which genomic drivers are present [59].

1.3.3 Secondary Myeloid Neoplasms

In the WHO 2022 guidelines, both AML/MDS that develops in the context of an inherited germline predisposition and AML/MDS that occurs as the result of prior chemotherapy (known as therapy-related AML, t-AML, therapy-related MDS, t-MDS, or a therapy-related myeloid neoplasm, t-MN), will be classified together as secondary myeloid neoplasms [9].

Whereas almost 10% of children that develop cancer did so in the setting of a germline genetic predisposition [60], it is estimated that approximately 25% of pediatric AML patients possess a germline genetic predisposition [61]. Inherited bone marrow failure syndromes commonly carry an increased risk of developing a myeloid neoplasm, with the highest risk among patients with Fanconi Anemia (15–20% cumulative incidence of AML by 40 years of age). Other important genes in which germline mutations predispose to myeloid neoplasms include *RUNX1* (44% lifetime risk), *CEBPA* (exact risk unknown but is highly penetrant, are present in 10% of AML patients with a biallelic *CEBPA* mutation), and *GATA2* (15% of pediatric MDS) [53].

Pediatric chemotherapy protocols have been modified and improved through prior decades to decrease t-MN. Nonetheless, approximately 0.5% of childhood cancer survivors treated with chemotherapy will still subsequently develop a t-MN [62–64]. However, the true risk of developing a t-MN is related to specific exposures to specific chemotherapy classes, with different patterns emerging: Prior treatment with Topoisomerase II inhibitors (such as Etoposide and anthracyclines) is associated with t-MNs that occur 1–3 years after exposure and often have *KMT2A* rearrangements. Prior treatment with alkylators (such as melphalan and cyclophosphamide) is associated with t-MNs that occur 5–7 years after exposure that more often have an MDS phase or have t-AML with myelodysplastic cytogenetic features (such as monosomy 5 and monosomy 7). The cumulative dose, frequency of dosing, interactions with other chemotherapy, and inherited genetic susceptibility all play a role in the likelihood of a t-MN developing after exposure to these classes of chemotherapy [65, 66]. While radiation therapy can also lead to (or contribute to) the development of t-AML, it does so at a reduced frequency, and patients with t-AML from radiation alone may have more bio-

logic similarities to de novo AML than chemotherapy-induced t-AML [67, 68]. In contrast to the relative rarity of pediatric t-MN, approximately 20% of all adult AML is t-AML [69]. Unfortunately, patients with t-MN have significantly worse outcomes than de novo AML/MDS, and HSCT once in remission should be the goal for therapy with curative intent [70].

1.3.4 Myeloid Sarcoma/Extramedullary AML

AML blasts are typically predominant in the bone marrow as this is the location where myeloid cells are formed and develop. However, AML blasts can accumulate in other tissues. When an extramedullary collection of AML blasts forms a solid tumor-like mass, these collections have been designated by the WHO as a myeloid sarcoma, although they also have been referred to as a chloroma, granulocytic sarcoma, and myeloblastoma. A myeloid sarcoma can arise anywhere, but have a propensity to emerge from bones with thin periosteum such as the orbit or vertebral bodies [18, 71], or even the skin (known as a cutaneous myeloid sarcoma, or more generally leukemia cutis) [72].

While most commonly myeloid sarcomas are present in the setting of concurrent systemic disease that includes the bone marrow, rarely a myeloid sarcoma can occur in the absence of bone marrow involvement, in which case it is referred to as an isolated, primary, or non-leukemic myeloid sarcoma [73]. In a children's cancer group (CCG) study of 1832 pediatric AML patients, 10.8% ($N = 199$) had a myeloid sarcoma present at diagnosis, of which only 0.7% ($N = 13$) had an isolated myeloid sarcoma [74]. For isolated myeloid sarcomas, it is generally expected that ultimately the disease will become systemic and that it should be treated similarly as systemic AML [73]. One possible exception are infants with isolated congenital myeloid leukemia cutis, in whom there are multiple case reports of spontaneous remission without recurrence [75].

1.4 The Incidence of AML: Trends, Exposures, Gender, and Ethnicity

1.4.1 Incidence Trends and Environmental Exposures

Globally, the incidence of AML has been gradually increasing over recent decades, with a more dramatic increase in the past decade in the United States. However, the majority of this increase is occurring among the elderly and correlates with the population as a whole becoming more skewed toward older ages. Nonetheless, there is an ongoing small but statistically significant increase in the incidence of childhood AML occurring each decade in the United States [76–79].

Developed countries also report higher incidences of AML compared to undeveloped countries [76]. While presumably much of this is related to increased aging populations and an improved ability to diagnose and track AML patients, a study of primarily adults from within a single developed country (Canada) identified that industrialized cities had significantly increased rates of AML potentially implicating exposure to pollutants as a contributing factor as well [80]. However, in contrast to adult cancers that develop slowly through a lifetime accumulation of genetic lesions (which often correspond to specific environmental exposures) [81], the effect of environmental exposures on the development of pediatric cancers and specifically leukemia is less clear, despite numerous studies on the topic [82]. Commonly cited environmental exposures associated with pediatric AML include ionizing radiation, hydrocarbons, and pesticides [83].

1.4.2 Gender and Ethnicity

During childhood, the incidence of AML between males and females is relatively equal. However, after 50 years of age, males begin to more frequently develop AML, which difference becomes increasingly prominent with older age [10].

Studies on the incidence of pediatric AML among different ethnicities have varied, but an increased incidence of AML among Asians and pacific islanders compared to white patients has been reported in two different studies from the California Cancer Registry [84, 85]. In the California Cancer Registry, there was a non-statistically significant increase in black patients, with no difference among Hispanic patients for AML overall [85]. However, the most striking correlation with ethnicity is the significantly higher incidence of the APL subtype among Hispanic children [86, 87].

1.5 AML Presentation, Therapy, and Outcomes

1.5.1 AML Presenting Symptoms

AML presenting symptoms are directly related to the burden and behavior of leukemic blasts. As AML blasts accumulate in the bone marrow and disrupt normal hematopoiesis, patients often present with symptoms of cytopenias, such as: paleness and fatigue related to anemia, bruising and bleeding related to thrombocytopenia, and fever related to either infection from neutropenia or as a result of cytokine signaling from the leukemic blasts themselves. Further, overcrowding of blasts in the bone marrow can result in bone pain or a limp. AML blasts (and particularly APL blasts) additionally have a propensity to trigger disseminated intravascular coagulopathy (DIC) in part due to expression of tissue factor on their cell surface [88]. Patients with hyperleukocytosis (commonly defined as a WBC > 100,000) are at particular risk of DIC, tumor lysis syndrome, and leukostasis resulting from increased intravascular viscosity (which commonly manifests itself with symptoms of decreased central nervous system (CNS) or pulmonary blood flow) [89]. Infiltration and accumulation of leukemic blasts in other organs can lead to hepatomegaly, splenomegaly, lymphadenopathy, myeloid sarcomas, and in monocytic forms respiratory distress from direct pulmonary invasion (which can be improved with the addition of dexamethasone) [90]. Less commonly, patients can also develop gingival hypertrophy, rashes, or subcutaneous nodules [18].

1.5.2 AML General Treatment Schema

After the diagnosis of AML has been confirmed, AML therapy is risk adapted such that patients with potentially less risk of relapse can receive less therapy, while patients at highest risk of relapse receive maximal therapy. Risk stratification and developing a plan of therapy rely on numerous factors, including: the underlying genetic drivers and AML subtype, initial response to therapy as measured by the amount of residual leukemia remaining after the first cycle of chemotherapy (known as measurable residual disease, MRD), the context in which the AML developed (such as AML that has developed in a Down Syndrome patient, or if AML is therapy related), or in the case of APL, the presenting white blood cell count.

The primary chemotherapy backbone of AML treatment relies on cytarabine and anthracyclines, which combination has been used for the treatment of AML since the late 1960s [91]. Prior to this time, a diagnosis of AML was essentially a death sentence [92]. Clinical trials for pediatric AML began in 1975 and significant progress was achieved with the AML-BFM 83 trial that introduced block scheduling of chemotherapy [93]. Current regimens for non-DS pediatric patients use four to five blocks of intensive chemotherapy, which can be curative alone for low-risk AML patients; however, high-risk AML patients typically proceed to HSCT after they obtain a first remission [94]. Moreover, obtaining cerebrospinal fluid at diagnosis to evaluate for invasion into the central nervous system and prophylactic treatment with intrathecal chemotherapy is routine in AML [95].

1.5.3 AML Outcomes and Recent Advances

Since the 1980s, overall survival rates have slowly risen for pediatric AML patients from approximately 50 to 70% [96–98]. In large part, this has been accomplished through improved salvage therapy for relapsed patients and through a reduction in treatment-related mortality with improved supportive care [93, 99–101]. Strong supportive care plays a significant role in survival as approximately 30% of patients receiving AML therapy will develop bacteremia, a potentially life-threatening infection [102], with modern AML regimens incurring a 3–15% incidence of treatment-related mortality [103]. Despite improvements in salvaging relapsed AML, overall survival after relapsed pediatric AML is only 40% [104]. Moreover, among survivors there is a significant increase in chronic health conditions of all kinds, with cardiotoxicity being an area of particular concern affecting 12% of pediatric AML long-term survivors [105, 106].

As current pediatric AML regimens already employ a maximal intensity of traditional chemotherapeutics, development of new therapies and treatment strategies will be essential to further improving cures and reducing the toxicity of treatment. Therapeutic advances over the past decade include refinements to risk stratification [36], Gemtuzumab ozogamicin (an anti-CD33 antibody-drug-conjugate) [107, 108], CPX-351 (a liposomal encapsulation of cytarabine and daunorubicin) [109, 110], targeted inhibition of FLT3 and IDH1/IDH2 [33, 34, 111, 112], venetoclax [113], and numerous forms of immunotherapy still in early phases of study [114].

A notable exception to the general schema of pediatric AML treatment and survival is APL. Demonstrating the potential of targeted therapy, standard-risk APL can now be treated without traditional chemotherapy using just ATRA and ATO alone, while achieving an event-free survival rate in excess of 95% with relatively little expected long-term toxicity from treatment [115, 116].

1.6 AML Inequalities

1.6.1 Adolescent and Young Adult (AYA) Patients

A group worthy of unique consideration are adolescent and young adult (AYA) AML patients, commonly defined as being 15–39 years of age at diagnosis. AYA AML patients have intermediate survival outcomes wherein they have an improved survival rate compared to older adults, but still fare significantly worse than younger pediatric patients [117–120]. When treated on pediatric studies, AYA AML patients have improved overall survival and increased rates of remission when compared to being treated on less intense adult AML regimens. However, this is partially offset by a significant increase in treatment-related mortality as it is more difficult for AYA patients to tolerate pediatric regimens than younger children [121]. As the increased risk of non-cancer mortality in AYA AML survivors can persist for decades [122], it is worth considering as to if uniquely tailored protocols that are neither purely pediatric nor adult should be created for AYA AML patients [120].

1.6.2 Racial Inequality in Outcomes

Race is known to have significant impacts in AML survival. Multiple studies have identified that black and Hispanic children have significantly worse outcomes in pediatric AML, which differences are not accounted for by underlying AML cytogenetics [123–127], and are particularly notable among black AYA patients [124]. These differences are not explained by compliance as AML chemotherapy is given intravenously while hospitalized, and one study was a single institution that was able to exclude factors related to insurance coverage in which the discrepancies persisted [126]. Some potential mediators of these outcomes include a reduced access to available HSCT donors [127], worse survival after HSCT [126], and increased early mortality/treatment toxicity [124, 127].

However, a study of adult AML patients that was intentionally designed to represent diverse urban neighborhoods found that the disparities in survival between white and black adult AML patients entirely disappeared when census tract data were controlled for [128]. A census tract represents a neighborhood with relatively homogenous social and economic outcomes and are often racially segregated. As such, census tracts can be used as a surrogate measure for structural racism (i.e., systemic disadvantage based in race), which can impact a patient's ability to benefit from health care. In this study, structural racism appeared to be the primary mediator of worse outcome among black adult patients. Such factors impacted by structural racism include a lack of access to health care prior to diagnosis (resulting in more prevalent undiagnosed chronic medical conditions at presentation or delayed presentation), decreased funding allocation for neighborhood infrastructure (which impacts roads, access to health care services, and employment opportunities that provide health insurance), decision support tools that are linguistically and culturally appropriate, timely transplant referral based on cultural assumptions and stereotypes, and so forth [128].

1.6.3 Global Inequality in Outcomes

Lastly, the aforementioned survival rates are only applicable to high-income countries with resources sufficient to accurately diagnose, risk stratify, and support pediatric AML patients through such intensive regimens. In low- and middle-income countries, outcomes can vary widely, but on the whole are substantially worse [129]. While progress has been made over the past two decades in decreasing global inequality for pediatric AML outcomes [130], it remains a significant area of concern when considering that almost 90% of the children in the world live in low- to middle-income countries and account for 95% of childhood cancer deaths [131].

1.7 Conclusion

Although AML is predominantly an adult disease, pediatric AML is a significant contributor to childhood cancer morbidity and mortality and is genetically distinct from adult AML. Pediatric AML is defined by recurrent genetic abnormalities that are most commonly structural chromosomal rearrangements such as t(8;21), inv(16), t(15;17), and *KMT2A* rearrangements, but additionally occurs in relation to myelodysplasia, Down Syndrome, prior therapy, or a germline predisposition. While AML therapy is risk stratified, with the potential exception of APL, the treatment is intensive for all comers and carries a significant risk of infection and long-term cardiotoxicity. AML subgroups that have achieved excellent outcomes include APL and ML-DS, but further work is significantly needed to improve outcomes, particularly for AYA patients, black and Hispanic patients, and for patients in low- to middle-income countries.

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2 Chromosomal and Genomic Alterations in Pediatric AML

Adam Lamble and Benjamin Huang

2.1 Introduction

The development of acute myeloid leukemia (AML) is characterized by an accumulation of chromosomal and genomic alterations within myeloid hematopoietic stem or progenitor cells that lead to impaired differentiation, sustained proliferative and survival advantages, and eventual outgrowth of a dominant clonal population. Studies in mouse models and more recent genomic analyses [1–4] support a model of leukemogenesis that revolves around the principle that two or more molecular alterations are required for transformation. Broadly speaking, somatic alterations associated with AML are divided into one of two classes. Class I alterations activate signal transduction pathways leading to increased proliferation and survival advantages and include mutations in RAS pathway genes (*NRAS*, *KRAS*, *PTPN11*, and *NF1*) and receptor tyrosine kinases (*FLT3* and *KIT*). Class II alterations lead to impaired hematopoietic differentiation and include chromosomal aberrations such as t(8;21) (resulting in the fusion oncogene *RUNX1::RUNX1T1*), inv(16) (*CBFB::MYH11*), t(15;17) (*PML::RARA*), 11q23 rearrangements resulting in *KMT2A* partner fusion oncogenes, and mutations in transcriptional regulators such as *CEBPA* and *RUNX1*.

Leukemia mouse models suggest that class I and II mutations cooperate to induce leukemia [5–10]. While unaccompanied class I mutations (expressed endogenously) result in myeloproliferative neoplasms [11–13], unaccompanied class II mutations abrogate normal hematopoiesis in utero [14, 15] or often result in no evidence of leukemia when expressed postnatally [16]. Retroviral overexpression systems with fusion oncogenes expressed from strong promoters can induce AML as sole drivers, but these models are less faithful in the genetic configuration and expression levels observed in human disease. Notable exceptions to this "two hit" paradigm have been observed [17–19], albeit with prolonged latency compared to their dual mutant counterpart models.

Several chromosomal alterations have long been associated with survival outcomes in AML [20], most notably the association of t(8;21) (*RUNX1::RUNX1T1*) and inv(16) (*CBFB::MYH11*) with favorable outcomes and monosomy 7 or 5, and del(5q) with poor responses, relapse, and low survival rates. Additional early studies found that specific somatic mutations are also prognostic, such as mutations in *NPM1* or *CEBPA* (favorable)

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and *FLT3* internal tandem duplications (ITDs) (unfavorable). As next-generation sequencing (NGS) studies have increasingly uncovered additional genomic alterations in AML, the number of prognostic biomarkers at diagnosis has increased substantially, which is a specific focus of this chapter.

While the roles that certain alterations play in leukemogenesis have not yet been well defined, others are becoming increasingly elucidated. As an illustrative example, recent studies indicate that gain of function *SAMD9* and *SAMD9L* germline mutations reduce cell cycle progression and lead to selective pressure that favors the outgrowth of AML clones that lose the mutant allele, often through the complete loss of chromosome 7 (or monosomy 7) [21], which represents an aneuploidy event associated with dismal survival outcomes in AML. Additionally, more recent transcriptome sequencing studies have successfully identified and helped characterize prevalent cryptic gene fusions in AML (e.g., *NUP98::NSD1*, *NUP98::KDM5A*, *CBFA2T3::GLIS2*, among several others) that are not detectable through more traditional assays, and ongoing efforts to gain a deeper understanding of the underlying biological basis and vulnerabilities of these alterations represent a critical need in the field of AML research.

2.1.1 Detection of Chromosomal Alterations

Cytogenetic alterations have been and remain a cornerstone for pediatric AML diagnosis and prognostication. Nearly two-thirds of pediatric AML cases are associated with a fusion oncogene, which is a stark contrast from AML diagnosed in older adults (Fig. 2.1). Within pediatric populations, age-based prevalence differences exist based on underlying fusion oncogene. While *KMT2A* rearranged, *CBFA2T3::GLIS2*, *NUP98::KDM5A*, among others, occur primarily within infant and very young children, core binding factor (CBF) AMLs (t(8;21) and inv(16)) occur more frequently in adolescents and young adults (Fig. 2.2). Structural alterations are frequently detected based on karyotype, and the development of fluorescent in situ hybridization (FISH) assays has resulted in increased sensitivity. Some fusion oncoproteins are the result of cryptic translocations not visible by conventional

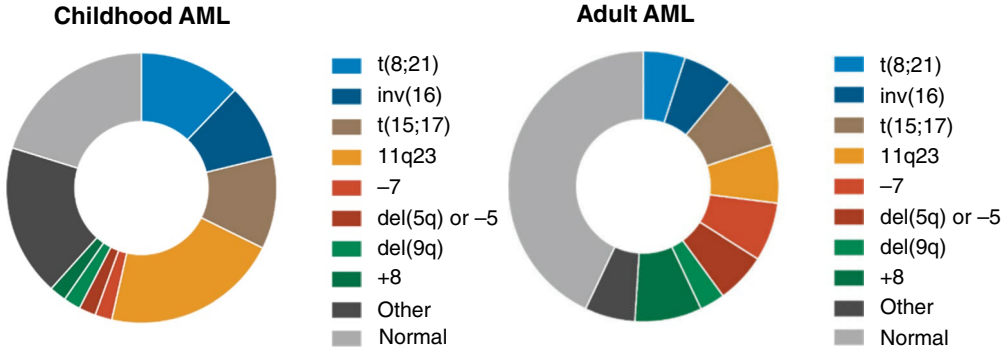

Fig. 2.1 Karyotypic alterations in childhood and adult AML. Chromosomal translocations are more prevalent in pediatric AML. Among the translocations that are identifiable by karyotype, t(8;21), inv(16), t(15;17), and 11q23 associated translocations are most notable. Despite being present in both children and adult AMLs, monosomy 7, del(5q), and monosomy 5 are more prevalent in adult AML

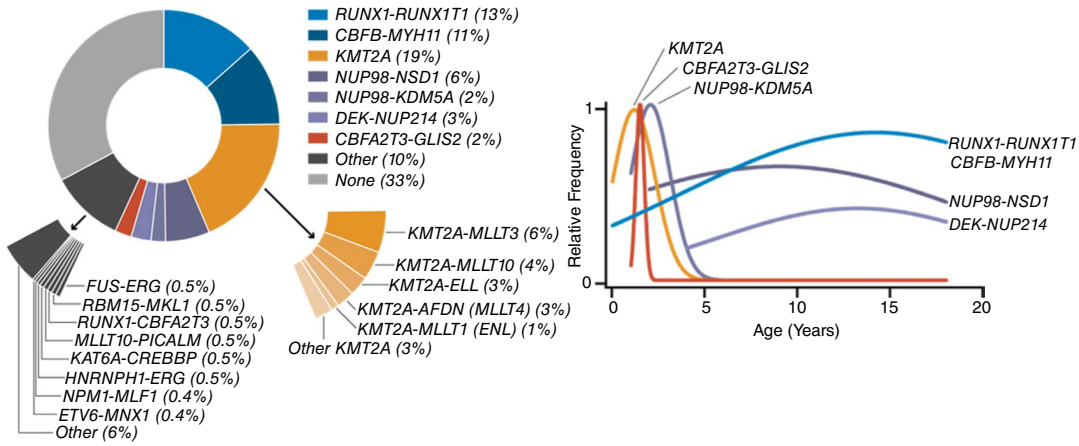

Fig. 2.2 Fusion oncogenes in pediatric AML. Prevalence of the most frequently identified fusion oncogenes (both non-cryptic and cryptic) as well as age-based associations

cytogenetic techniques. Newer FISH probes targeting these alterations and increased utilization of NGS has improved their clinical detection. The detection of these fusions (e.g., *NUP98::NSD1*, *NUP98::KDM5A*, and *CBFA2T3::GLIS2*) is of critical importance given that several are associated with very poor survival outcomes [22, 23]. A normal karyotype is found in about one-quarter of pediatric AML cases and are believed to arise due to either the presence of the aforementioned cryptic translocations or the presence of somatic driver mutations [24, 25].

2.1.2 Detection of Genomic and Transcriptomic Alterations

Whole genome sequencing (WGS) and transcriptome sequencing (RNA-seq) provide comprehensive coverage of the cancer genome at a single base resolution (WGS) (Fig. 2.3), sensitive fusion oncogene detection (RNA-seq) (Fig. 2.2), and detailed gene expression data (RNA-seq). The complementary results provided by these two NGS methodologies represent the most comprehensive interrogation of cancer genomes to date. These sequencing efforts, which were facilitated by the collaborative efforts of the Children's Oncology Group (COG) National Cancer Institute (NCI) TARGET AML Initiative [1] and the St. Jude and Washington University Pediatric Cancer Genome Project (PCGP) [2, 26], have provided new biological insights into the molecular basis of leukemia, more accurate molecular subtype relapse risk and survival prediction, and promising candidate therapeutic targeting approaches. For instance, mutations that are common in adults (e.g., *DNMT3A*) were conspicuously absent from this cohort. Conversely, as discussed above, AML in children, adolescents, and young adults is characterized by frequent fusion oncogenes and much higher prevalence of signaling mutations (e.g., *NRAS*, *KRAS*, *PTPN11*, and *KIT*), highlighting the need for research and molecular therapeutic approaches specific for these distinct pediatric AML subtypes. The remainder of this chapter focuses on recent advances based on these efforts, as well as future and ongoing directions.

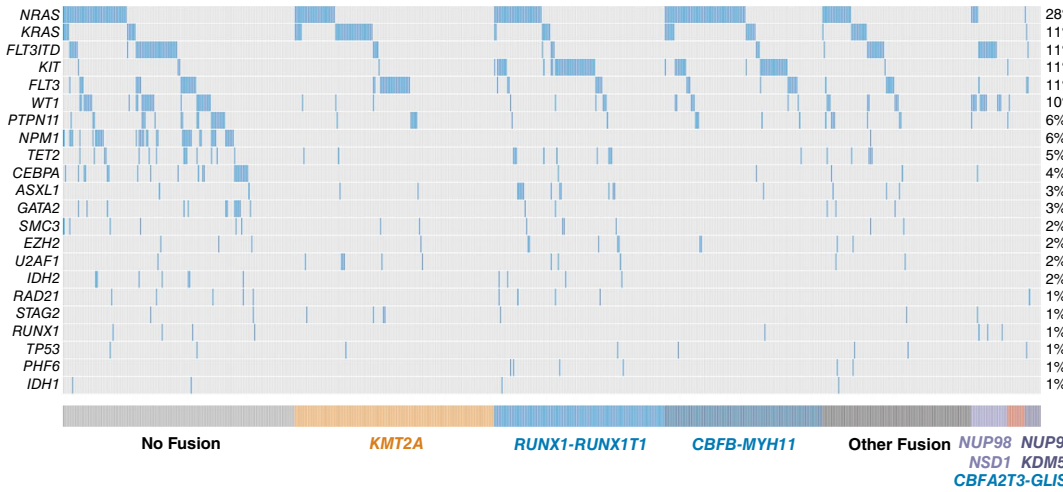

Fig. 2.3 Genomic landscape of pediatric AML. Somatic mutations and fusion oncogenes associated with pediatric AML and identified through NGS. (Based on Bolouri et al. [1])

2.2 Chromosomal Alterations

2.2.1 Core Binding Factor Fusions

Core binding factors (CBFs) RUNX1 and CBFB are hematopoietic transcription factors required for normal hematopoiesis. Oncogenic transforming translocation events in CBF genes lead to altered DNA binding, disruption of normal hematopoietic transcription programs, and resultant maturation arrest [27]. Core binding factor translocations t(8;21) (*RUNX1::RUNX1T1*) and inv(16) (*CBFB::MYH11*) are present in 25% of pediatric patients at diagnosis, representing the largest subgroup in pediatric AML (Table 2.1). They are both more prevalent in adolescents and young adults compared to younger children, and both are rare for infants. While typically associated with a favorable prognosis, there is emerging evidence that the co-occurrence of specific molecular alterations is associated with worse outcomes [28, 29].

2.2.1.1 *RUNX1::RUNX1T1*

The translocation t(8;21)(q22;q22) results in the formation of the *RUNX1::RUNX1T1* fusion gene. *RUNX1::RUNX1T1* is the most common fusion oncogene in pediatric AML, present in 10–12% of childhood AML cases [24, 30]. It is associated with the French-American-British (FAB) M2 subtype and leukemia blasts often contain azurophilic granules, rare Auer rods, and aberrant expression of CD19 and CD56. More than half of cases have one or more additional cytogenetic abnormality, including loss of X or Y chromosome, del(9q), or trisomy 8. Somatic co-occurring mutations in *KIT*, *RAS*, and *ASXL* are common [31]. Clinical outcomes for these patients are favorable. In addition, relapsed patients are salvageable suggesting this subtype is amenable to the graft versus leukemia effects of hematopoietic stem cell transplant (HSCT). Specifically, co-occurrence of exon 17 *KIT* mutations (but not exon 8 *KIT* mutations) is associated with worse outcomes. Notably, the modulation of exon 17 *KIT* mutations may be overcome with intensification of upfront therapy, including the addition of gemtuzumab ozogamicin [32].

2.2.1.2 *CBFB::MYH11*

The inversion inv(16)(p13;q22) and the less common translocation t(16;16)(p13;q22) both result in the formation of the *CBFB::MYH11* fusion gene. This subtype occurs in 7–11% of childhood cases. It is associated with the FAB M4 subtype and in certain cases eosinophilia. Additional co-occurring cytogenetic abnormalities include trisomy 22, trisomy 8, and del(7q) [33]. Similar to

Table 2.1 Common chromosomal alterations in pediatric AML

Chromosomal alteration	Gene fusion	Frequency	Prognosis	Reference
t(8;21)(q22;q22)	*RUNX1::RUNX1T1*	10–15%	Favorable	[2, 31]
inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	*CBFB::MYH11*	5–10%	Favorable	[2, 137]
11q23[a]	*KMT2A* rearrangements	15–20%	Variable	[49, 138]
t(15;17)(q24.1;q21.2)	*PML::RARA*	5–10%	Favorable	[139]
11p15	*NUP98* rearrangements	6–10%	Poor	[64]
t(5;11)(q35;p15)	*NUP98::NSD1*	3–4%	Poor	
t(11;12)(p15;p13)	*NUP98::KDM5a*	1–2%	Poor	
t(6;9)(p22;q34)	*DEK::NUP214*	<2%	Poor	[76]
inv(16)(p13.3;q24.3)	*CBFA2T3::GLIS2*	2–3%	Poor	[56]
t(1;22)(p13;q13)	*RBM15::MLK1*	<1%	Intermediate	[140]
t(7;12)(q36;p13	*MNX1::ETV6*		Poor	[77]
Inv (3)(q21q26.2) or t(3;3)(q21;q26.2)	*GATA2::MECOM (EVI1)*	1–2%	Poor	[24]
t(8;16)(p11;p13)	*KAT6A::CREBBP*	1–10%	Poor	[71]
t(3;5)(q25;q35)	*NPM1::MLF1*	<1%	Poor	[84]
t(16;21)(p11;q22)	*FUS-ERG*	<1%	Poor	[79]
Monosomy 5, del(5q)	Not applicable	1.2%	Poor	[141]
Monosomy 7	Not applicable	3%	Poor	[142]

[a]See Table 2.2 for specific *KMT2A* partner rearrangements

RUNX1::RUNX1T1, the favorable prognosis typically conferred by this lesion is negatively impacted by the co-occurrence of exon 17 *KIT* mutations. In addition, specific *CBFB::MYH11* transcript subtypes [29] have been associated with a significant increase in relapse rates.

2.2.2 Unbalanced Chromosomal Abnormalities

Unbalanced chromosomal abnormalities, including partial or total gains and losses of chromosomes, are relatively common in children, occurring in up to 40% of pediatric AML cases [34]. Similar to the balanced abnormalities, these gains or losses can be detected by conventional cytogenetic techniques, but other techniques such as comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP)-array can be used for more sensitive detection of shorter-segment aberations [35]. While common, the majority of these events do not appear to impact outcomes and are considered prognostically neutral. The most common unbalanced abnormality is trisomy 8, which is found in 10–15% of pediatric AML and always co-occurring with other cytogenetic or molecular alterations. Monosomy 7, del(5q), and monosomy 5 are notable for their association with dismal outcomes [24, 25].

2.2.3 KMT2A-Rearranged Fusions

Located at 11q23, lysine methyltransferase 2a is encoded by the gene *KMT2A* (previously known as *MLL*) and is responsible for regulating gene expression during early development and hematopoiesis. *KMT2A* is frequently rearranged with one of a family of partners to form a fusion oncogene class that is highly prevalent within infant onset acute leukemias (both infant AML and B acute lymphoblastic leukemia or B-ALL) (Table 2.2). The most prevalent *KMT2A* translocation is *KMT2A::MLLT3* and its transformation capability was appreciated early on [9, 17, 18, 36]. While the prevalence of *KMT2A*-rearranged AML is highest during infancy (50%), the diagnosis remains commonplace before 3 years of age (35–40%), and then becomes rare thereafter (10–20%).

Similar to other structural alterations, *KMT2A* rearrangements can often be detected based on karyotype and FISH assays. Notably, the most frequently utilized *KMT2A* FISH assays use a break-apart method resulting in high sensitivity