

Advances in treating acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) arises within the bone marrow from a malignant hematopoietic progenitor cell. Though AML is still often fatal, cure rates overall continue to improve incrementally yet steadily, primarily for two reasons: first, insights into the pathogenesis of AML over the last several decades have led to the development of a relatively sophisticated classification scheme that allows more nuanced risk stratification to guide treatment choices; second, improvements in stem cell transplantation have allowed many more patients to take advantage of this highly effective therapeutic technique. Improvements in overall survival for patients with AML are expected to continue rising because of the anticipated introduction of targeted therapies into this treatment platform.

Introduction

AML, the most common type of acute leukemia in adults, has an annual overall incidence of 3.8 cases per 100,000 in the US and Europe [1–3]. In the US, 18,860 cases and 10,460 deaths are projected in 2014 [4]. Although it can occur in children and adults, AML is primarily a disease of the elderly, with an incidence of 15 cases per 100,000 for those over 60 [1]. Unfortunately, the 5-year overall survival (OS) in patients older than 75 is less than 10% and has not improved in the last 30 years [5]. In contrast, there were steady gains in treatment of patients younger than 60, with the 5-year OS rising from less than 10% to 50% for patients aged 25 to 39 [6]. Advances in treatment, as reflected in survival gains, have been modest in the last several decades, reflecting the complexity and aggressive nature of AML. Pediatric disease accounts for only 6% to 7% of AML cases and has a biology somewhat distinct from that of adult disease. There is a significantly lower incidence of more aggressive, high-risk disease [1,7]. The disease still poses a critical challenge to pediatric oncologists but, in children, long-term survival rates are greater than 60%, which is significantly higher than in adults. Although pediatric AML occasionally presents in tandem with inherited syndromes that manifest in childhood, children overall have fewer comorbidities and

tolerate intensive therapy better than adults. Owing to these distinctions, this article will focus on AML in adults.

AML is a malignancy arising within the bone marrow, in which leukemia cells proliferate uncontrollably in association with a disruption of normal hematopoiesis or blood cell production. At presentation, the marrow of a patient with AML is occupied with approximately 10^{12} leukemia cells. Contributing factors to the low survival rates are the acuity and severity of illness at diagnosis. Patients with AML usually present because of complications of disordered hematopoiesis: bleeding, fatigue, refractory infections, or the clinical consequences of an extremely high white blood cell count: difficulty breathing, confusion, or other symptoms of organ failure. Beyond supportive care to stabilize patients, definitive treatment is typically divided into two phases. Induction therapy, the initial therapy meant to induce a disease remission, consisting of DNA-damaging agents (most commonly cytarabine, a nucleoside analogue, combined with an anthracycline such as daunorubicin), can frequently cause apoptosis in the majority of the leukemic cells, and most patients achieve a remission. Unfortunately, disease will relapse in almost all patients unless it is eliminated by additional therapy [1,8]. Further treatment attempting to consolidate

remission into cure, “consolidation therapy”, consists of additional chemotherapy or bone marrow stem cell transplantation (SCT). In patients younger than age 65, although induction chemotherapy can generally yield remission rates of 70% to 80% [9], at least half of these patients eventually relapse and ultimately die without SCT. Even with SCT, over one third will relapse [10,11]. Despite the current dismal median survival for AML of approximately one year, OS for younger patients with AML has been rising steadily [6]. To some degree, this improvement can be attributed to advances in supportive care.

Over the last few decades, developments in supportive care have made chemotherapy more tolerable. More potent antiemetic agents, such as the selective 5-HT₃ receptor antagonists, ameliorate chemotherapy-induced nausea and vomiting [12]. Rasburicase prevents uric acid crystallization in the kidney, one of the more toxic effects of the rapid proliferation of leukemia cells [13]. Prevention and treatment of infections are arguably the most significant improvements in supportive care. Routine prophylaxis against fungal infections is associated with increased survival [14,15]. The anti-infectious armamentarium has been further fortified with new antimicrobials against virulent microbes, such as pseudomonas and resistant staphylococcus [16]. In addition, new formulations of older agents that facilitate drug delivery and that are less toxic have enabled the treatment of a broader population [17,18]. These advances in supportive care enable patients to withstand prolonged rigorous treatment with chemotherapy and SCT, contributing to improved outcomes. In large part, though, the steady gains in long-term survival in AML have come from advances in SCT methods and also from a better understanding of which patients benefit from intensive SCT, which derived from greater insight into the pathogenesis of the disease.

Pathogenesis of acute myeloid leukemia

Our understanding of the pathogenesis of AML has evolved over the years. The existence of a cancer stem cell was first established in AML. Leukemia appears to retain some semblance of normal hematopoietic biology. The leukemia stem cell (LSC) theory posits that rare stem cells with self-renewal capacity give rise to partially differentiated progeny that comprise the bulk of the leukemia but possess only limited proliferative potential and do not have the capacity to initiate or maintain disease [19,20]. Eradicating these bulk cells is not sufficient to cure the disease, as the LSCs, a more drug-resistant population, persist and will re-populate the marrow, causing disease relapse in almost all patients unless eliminated by additional therapy [21–23]. The identification of this purported LSC that initiates relapse

in patients has proven elusive. However, there are now preliminary data supporting this hypothesis, reporting a clinically relevant LSC population: a rare population of cells that have leukemic characteristics yet that are phenotypically and functionally more primitive than the bulk leukemia cells and that are associated with relapse in patients with AML and are not found in healthy patients [24].

Despite its limited clinical application thus far, this stem cell hypothesis provided a crucial framework in which to incorporate a growing body of genomic data, beginning with the identification of recurrent chromosomal abnormalities associated with certain disease subtypes [25]. The list of so-called driver mutations, unlike that of solid tumors, is relatively modest in AML [26]. Whole genome and whole exome studies performed on banks of AML specimens indicate that, although the total number of mutations that can be found in AML is quite large, only about 10 to 20 mutations commonly occur in coding regions and are relevant to disease pathogenesis. Furthermore, any single AML sample has relatively few of these recurring mutations [8,27,28]. A simple two-step mutation hypothesis first proposed by Gilliland and Griffin [29], in which a growth factor pathway mutation combined with a differentiation block led to AML, has subsequently been modified to the current working model, in which an “initiating” mutation, which might be a translocation or a coding sequence mutation, occurs in a hematopoietic stem cell, initiating clonal expansion [27]. Subsequently, within this expanding clone, one or more cooperating mutations occurs, completing the transformation process. Within this malignant founder clone, different sub-clones may develop, rendering the disease oligoclonal at presentation [27,28,30]. The types of initiating and cooperating mutations within the founding clone determine the phenotype of the disease at presentation [27]. Furthermore, the mutational profile may evolve through the course of disease progression. The clone may gain mutations, randomly as a matter of time or as a result of mutagenic potential of previous chemotherapy. A dominant sub-clone may evolve, possibly because of varying sensitivities to previous treatment. Ultimately, the founding clone is never completely eradicated. These alterations may or may not be biologically relevant [31,32].

This current model of AML pathogenesis, which is derived from the summation of molecular and clinical studies spanning decades, represents the most important recent advance in the therapy of AML because it serves as an immediately useful guide for recognizing a patient’s prognosis, which then guides therapy decisions. If a remission is achieved after induction therapy, the decision

to consolidate a patient with an SCT, rather than more chemotherapy, is based on evolving algorithms incorporating the genetic lesions and predicted disease behavior. The following illustrates how this information shapes our management of AML.

Risk stratification

Initial risk stratification of AML divided the disease into the following major categories: intermediate-risk AML with normal karyotype, AML with favorable-risk karyotype, AML with unfavorable-risk karyotype, and AML arising out of antecedent myelodysplasia (MDS/AML). Subsequently, other mutations, such as *FLT-3* and *NPM1*, which further delineate disease behavior and prognosis, were identified.

Acute myeloid leukemia with intermediate-risk karyotype

These cases are defined as either having no karyotypic abnormalities by G-banding or fluorescence *in situ* hybridization (FISH) or having only one or two abnormalities not categorized as high- or low-risk. This is the largest single category of AML but in fact is made up of many different variants, each with a unique molecular signature. In many cases, the clinical behavior and prognosis vary according to the particular mutations present, altering treatment decisions within this group [28].

FLT3/isocitrate dehydrogenase

Internal tandem duplication mutations in the *FLT3* gene are found in roughly 20% of AML cases and in over a third of AML cases with a normal or intermediate karyotype. The mutations result in aberrant and constitutive activation of the tyrosine kinase function of *FLT3*, resulting in inhibition of apoptosis and uncontrolled proliferation [33]. Not surprisingly, these mutations are associated with a particularly aggressive AML variant associated with a poor prognosis. In the current molecular model, *FLT3/ITD* mutations are believed to act as cooperating rather than founding mutations and frequently occur with *NPM1* and DNA methyltransferase 3A (*DNMT3a*) mutations [34]. Even so, their presence seems to outweigh other mutations in that they convert a case with an otherwise favorable genetic lesion into an unfavorable one. Patients with *FLT3/ITD* AML will often respond to initial induction therapy and achieve a remission, but early relapse is common. The disease that emerges at relapse is frequently clonal, highly addicted to *FLT3* signaling, and generally rapidly lethal. Although the development of *FLT3* tyrosine kinase inhibitors is under clinical development, they have not supplanted the need for allogeneic transplant, which is associated with distinctly improved outcomes, although the data supporting this approach are retrospective [35].

As these patients tend to relapse early, the ability to proceed quickly to SCT immediately after induction is essential [36].

NPM1

Mutations in the nucleophosmin gene result in aberrant localization of this nuclear protein to the cytoplasm. Their exact role in malignant transformation is not completely understood. When present, they are detectable in all sub-clones, with only rare exceptions, suggesting that these mutations behave if not as initiating mutations [26,28,37–39] then as early primary leukemogenic events [40]. When not found with a coexisting *FLT3/ITD* mutation, *NPM1* mutations can be viewed as a relatively favorable prognostic indicator and transplant is usually not necessary [41].

C/EBP α

CCAAT-enhancer-binding protein alpha (*C/EBP* α) is a transcription factor central to differentiation programs in a number of tissue types, including myeloid hematopoiesis. Mutations in *C/EBP* α are found in 5% to 15% of cases with normal karyotype [42] and confer a survival advantage [43] but only in the case of double or homozygous *C/EBP* α mutations in which there is no wild-type expression. This double allele mutation leads to both a differentiation block and enhanced proliferation [40].

Other mutations

Studies have demonstrated that methylation of cell regulatory genes is associated with gene silencing. In AML, several genes that control differentiation and proliferation have altered methylation patterns [44,45]. Both isocitrate dehydrogenase (*IDH1* and *IDH2*) and *DNMT3A* encode enzymes that promote DNA methylation, resulting in gene silencing and maintenance of proliferative homeostasis [38]. *IDH* mutations result in the production of an aberrant enzyme that ultimately upregulates methylation, inhibiting differentiation [46]. The impact of these mutations on survival is unclear. *DNMT3A* mutations result in loss of enzymatic activity and decreased DNA methylation, presumably discontinuing suppression of genes with leukemogenic potential [38,47]. However, their complete mechanism of action remains elusive as altered methylation patterns have not been uniformly demonstrated in cohorts of patients with *DNMT3A*-mutated AML [48,49]. These mutations are associated with poor survival [50].

Acute myeloid leukemia with favorable-risk karyotype

These cases are composed of acute promyelocytic leukemia (APL) and the so-called core-binding factor (CBF)

leukemias, in which a subunit of a critical myeloid transcription factor is altered by translocation.

Acute promyelocytic leukemia

These cases are associated specifically with the translocation *PML/RARA*, causing production of an oncoprotein in which a retinoic acid receptor subunit (RARA) is fused with a myeloid transcription factor (PML), with associated co-repressor proteins preventing the normal function of PML. The result is a block in myeloid differentiation at the promyelocyte stage, with the malignant cells often inducing activation of clotting factors and disseminated intravascular coagulation [51]. Patients with APL are treated with all-trans retinoic acid (ATRA), which releases the block in differentiation, combined with either chemotherapy or arsenic, which causes degradation of the oncoprotein itself [52]. This combination targeted therapy is associated with very high cure rates for patients with APL and is a superb example of treatment that directly affects the specific pathologic anomaly arising from the genetic profile of a tumor [53].

Core-binding factor leukemia

These are composed of cases with chromosomal translocations involving a subunit of CBF. In t(8;21), the gene coding for the alpha subunit of CBF (also known as *AML1* or *RUNX1*) is fused to the *ETO* gene, interfering with normal CBF function and leading to a block in myeloid differentiation [54]. In AML with inv (16), the beta subunit of CBF is fused to the smooth muscle myosin heavy chain, leading to sequestration in the cytoplasm and again a block in differentiation [55].

CBF translocations are very favorable prognostic mutations and are treated with combination chemotherapy only [8]. In fact, recent incorporation of gentuzumab ozogamicin into the chemotherapy regimen has resulted in long-term survival rates that are approaching those observed with APL [56]. Mutations in *c-Kit* often occur in CBF AML, and although some posit that this worsens prognosis, their impact is not completely clear [57,58].

Acute myeloid leukemia with unfavorable-risk karyotype

This category of AML is characterized by recurrent chromosomal abnormalities, including translocations, unbalanced rearrangements, gains or losses of whole chromosomes, or multiple concomitant abnormalities, referred to as a complex karyotype. In some cases, there are distinctive clinical features, but the common characteristic is their association with very poor survival rates, regardless of any coexisting mutations [8,25,59]. If a remission can be achieved at all, prompt consolidation with allogeneic transplant is the only hope for a cure [9]. Some of the various karyotypes and proposed molecular mechanisms underpinning their leukemogenic potential are summarized in Table 1. In general, these lesions alter the proliferation and differentiation of hematopoietic cells [8,25,59–65].

Myelodysplasia/acute myeloid leukemia

This variant of AML evolves from the myelodysplastic syndromes, antecedent bone marrow disorders which manifest as the production of blood cells with both abnormal form and function. These leukemias have a

Table 1. Selected unfavorable-risk karyotypes

Chromosomal abnormality	Genes involved	Effect	Comments
inv3	<i>EVII</i> gene activation	Enhanced proliferation and decreased differentiation	
del(5q) or monosomy 5	Unclear but likely a tumor suppressor gene located on 5q31	Likely decreased TSG expression	PITX1, CDC25, HSPA9, EGRI, CTNNA1, and THRCP
t(6;9)	<i>DEK-NUP</i>	Abnormal protein transport in nucleus	
del(7q) or monosomy 7	Unclear but may involve transcription factor <i>CUX1</i>	Altered regulation of proliferation	Abnormalities of chromosome 7 are the most common in AML.
+8	Overexpression of <i>MYC</i>	Inhibition of apoptosis; permissive cell growth and proliferation	
t(11q23)	Mixed lineage leukemia gene	Histone methyltransferase; promiscuous transcription of the partner gene	Associated with t-MN due to previous topoisomerase inhibitor agents
+13	<i>FLT3</i>	Increased expression via gene-dosage effect	Associated with <i>AML1 (RUNX1)</i> mutations
t(9;22)	<i>BCR-ABL</i>	Constitutively activated tyrosine kinase affecting proliferation, apoptosis, and differentiation	Also associated with kinase-independent activity
Complex Monosomal Karyotype	3 or more chromosomal abnormalities 2 or more monosomies or 1 paired with a structural abnormality		Often associated with mutated p53 TSG

AML, acute myeloid leukemia; t-MN, therapy related myeloid neoplasms; TSG, tumor suppressor gene

very different mutation profile than that of so-called “de novo” AML and carry a worse prognosis than virtually any other sub-group of AML [66]. The only chance at long-term survival is with an SCT [9]. Because MDS/AML usually occurs in older patients, curative treatment was not available to a large portion of this population until recently, when SCT was feasible in older patients. A relatively recent change in the treatment of MDS/AML is the employment of the DNA hypomethylating agents azacitidine and decitabine. These agents offer a less intensive treatment option than traditional cytotoxic chemotherapy. Low doses of azacitidine and decitabine can reverse the inactivation of genes that are silenced via hypermethylation, leading to restoration of differentiation and regulated proliferation [67,68]. Unfortunately, these genetic and cellular changes are not durable. Initially used in the treatment of MDS, these drugs are modestly effective and induce transient responses in some patients with AML [69,70]. Taken together, these insights into the biology of AML, allowing more nuanced risk stratification, serve as an immediately useful guide to the choice of consolidation treatment, either SCT or multiple cycles of standard chemotherapy.

Improvements in stem cell transplantation

Another important advance in AML therapy is the development of more sophisticated SCT techniques that have both ameliorated toxicities and allowed more patients to undergo the procedure. Originally, SCT developed as a method of eradicating a patient’s bone marrow with high-dose chemotherapy and then rescuing bone marrow function by infusing marrow stem cells collected from an HLA-matched donor. The immunologic condition known as graft-versus-host disease (GVHD) is a systemic process mediated by donor T cells engaged in an attack on host tissues [71]. Gradually, it was recognized that this allogeneic immune response, not simply the high-dose chemotherapy, was responsible for a significant portion of the anti-leukemic effect. If the patient survived both the high-dose chemotherapy and GVHD, cure of otherwise refractory disease might be achieved [72,73]. Modification of conditioning regimens and immunosuppression have decreased GVHD while maintaining immune function, decreasing both graft rejection and GVHD. Additional advances in methods used to control GVHD further improved tolerability, allowing reduced intensity conditioning (RIC) and mismatched donors. Reducing the intensity of the chemotherapy prior to stem cell infusion enabled older patients and others not fit for the traditional intensive conditioning to undergo SCT [73,74]. Finally, the use of alternative donors, in which the source of the rescuing stem cells is either a partially HLA-matched donor or umbilical cord blood, has significantly increased the

number of patients with an acceptable donor. Only one third of patients have a matched sibling, and only 50% have a potential matched unrelated donor (MUD), and candidates who are not of Northern European descent have even fewer MUD options. Because biologic parents and children and approximately half of siblings will be a haploidentical match, greater than 95% of patients have a haploidentical relative who is an appropriate donor. In addition, finding a umbilical cord blood (UCB) or haploidentical donor typically takes less time than finding an MUD, a salient fact because relapse of aggressive AML occurs quickly [75–77]. As AML is most commonly seen in older patients, curative treatment was not available to a large portion of these patients until recently, when allogeneic transplant became available to an older patient population. As older patients are often less fit and have older siblings, who are not ideal donors, recent advances in SCT with both the use of RIC, which enlarges the population of eligible patients, and the use of haploidentical donors, which expands the donor pool, may have a significant impact in finally extending survival for patients over the age of 60.

These two advances, a classification scheme based on a model of pathogenesis and improvements in SCT technique, are central to our current management of AML and likely will be the source of continued improvements in outcomes. Other areas of investigation are under way as well.

Future risk stratification efforts and “minimal residual disease”

There is still great heterogeneity in outcomes within populations defined by cytogenetic and mutation abnormalities. For instance, AML with CBF abnormalities is considered low-risk, yet almost half of these patients relapse after standard chemotherapy [8]. Therefore, attempts to further stratify these groups, in order to identify patients at higher risk of relapse in need of SCT upfront, are under investigation. Considerable effort has been made to identify a clinically relevant population of “minimal residual disease” (MRD), which is leukemia identified at very low levels undetectable by standard methods currently used to define remission. Methods used to identify MRD employ polymerase chain reaction detection of chromosomal alterations, more sophisticated flow cytometry that can detect minute populations, and attempts to identify novel rare populations within the leukemic clone that may predict relapse [24,78,79]. Identification of a clinically relevant MRD population that predicts relapse would enable clinicians to identify patients after induction who are at higher risk of disease recurrence and then modify consolidation treatment accordingly.

The future: targeted therapy

The next quantum step forward in improving outcomes for patients with this disease most likely will be from the introduction of targeted therapies into the existing treatment algorithms. Currently, ATRA and arsenic are the only treatments that are truly targeted to a specific mutation. However, small-molecule inhibitors of the FLT3 tyrosine kinase are under phase 3 development and show promising clinical activity. One or more of these drugs likely will be incorporated successfully into chemotherapy and transplant regimens for patients with *FLT3/ITD* AML in the near future [35]. Likewise, *IDH* inhibitors have been shown to have activity in pre-clinical models of *IDH*-mutated AML. Furthermore, recent clinical data suggest that inhibitors of *IDH2* can induce remission in some patients with relapsed and refractory *IDH2*-mutated AML [80].

Conclusions

Our approach to how aggressively to treat AML with the existing combinations of chemotherapy and SCT is modified almost yearly. Although transplant techniques continue to be refined, it seems unlikely that any more significant improvements in outcomes can be squeezed out of traditional genotoxic chemotherapeutic agents. The next real improvements in this field are very likely to come from attempts to further exploit our increasing knowledge of the biology of AML, with the development of more sophisticated targeted therapies. The hope is that these new therapies will be both more tolerable and efficacious. As our knowledge of the biology of AML continues to expand, it is likely that steady favorable progress will continue in our treatment of these patients.

Abbreviations

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; CBF, core-binding factor; *C/EBP α* , CCAAT-enhancer-binding protein alpha; *DNMT3A*, DNA methyltransferase 3A; GVHD, graft-versus-host disease; *IDH*, isocitrate dehydrogenase; LSC, leukemia stem cell; MDS, myelodysplastic syndromes; MRD, minimal residual disease; MUD, matched unrelated donor; OS, overall survival; PML, promyelocytic leukemia; *RAR α* , retinoic acid receptor alpha; RIC, reduced intensity conditioning; SCT, stem cell transplantation.

Disclosures

The authors declare that they have no disclosures.

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