Secondary Adult Acute Myeloid Leukemia: a Review of Our Evolving Understanding of a Complex Disease Process

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Opinion Statement

Secondary AML (s-AML) encompasses AML evolving from myelodysplasia (AML-MDS) and treatment-related AML (t-AML) after exposure to chemotherapy, radiation, or environmental toxins. S-AML has traditionally been considered a devastating disease, affecting a vulnerable population of heavily pretreated, older adults. A limited understanding of disease pathogenesis/heterogeneity and lack of effective treatments have hampered overall improvements in patient outcomes. With the recent understanding that the secondary nature of sAML does not by itself incur a poor prognosis and incorporation of cytogenetics and molecular genetics into patient care and the advancement of treatment, including improved supportive care, novel chemotherapeutics agents, and nonmyeloablative conditioning regimens as part of allogeneic hematopoietic cell transplantation (HCT), modest gains in survival and quality of life are beginning to be seen among patients with s-AML.

Introduction/Epidemiology

Although one of the least common types of cancer in the USA (incidence, 3–5 cases per 100,000), acute myeloid leukemia (AML) is one of the most lethal types of cancer and is the most common type of acute leukemia seen in adults [1–5]. In 2014, an estimated 18,860 people were diagnosed with AML, and 10,460 died secondary to this disease. Secondary leukemia (s-AML) accounts for 10–20 % of AML diagnoses and is seen most commonly among older adults (median age at diagnosis, 61 years) [6–8]. S-AML encompasses both patients who have AML

evolving from previous myelodysplasia (AML-MDS) or other myeloid stem cell disorder and patients who develop treatment-related AML (t-AML) after exposure to chemotherapy, radiation, or environmental toxins. Both types of AML lie along a continuum of disease and are categorized based on the 2008 World Health Organization (WHO) classification system as therapy-related myeloid neoplasms (t-MN) [9].

Presentation/Diagnosis

Similar to patients with other types of acute leukemia, those with s-AML typically present over a period of several months with symptoms related to complications of bone marrow failure and pancytopenia, such as fatigue, weakness, infections, and/or excessive bleeding [10]. As with other types of AML, s-AML is diagnosed by the presence of blast forms in at least 20 % of the total cells of the bone marrow aspirate (from a 500 cell differential count). The blast cells must be of myeloid origin as demonstrated by either the presence of Auer rods, myeloperoxidase cytochemical positivity, or the presence of sufficient myeloid markers. These markers can be recognized by immunophenotyping, such as cluster of differentiation 13 (CD13), CD33, CDw65, and CD117 positivity. Exceptions to the diagnostic criteria, where 20 % blasts are not required for diagnosis, include myeloid sarcomas and AML with recurrent genetic abnormalities, such as those with t(8;21), inv(16), or t(15;17) [11].

AML-MDS

The diagnosis of AML-MDS is made when the diagnosis of AML occurs in a patient with a previous history of MDS who has hematologic and cytogenetic features consistent with MDS. Under the microscope, patients with AML-MDS typically have dysplastic neutrophils (i.e., hypogranular cytoplasm, hyposegmented nuclei, and/or bizarrely segmented nuclei), dysplastic erythrocytes (i.e., megaloblastoid shape, karyorrhexis, nuclear irregularity, nuclear fragmentation, multinucleation, ring sideroblasts, cytoplasmic vacuoles, periodic acid-Schiff positivity), and dysplastic megakaryocytes (i.e., small, nonlobulated, widely separated nuclei) [10–12]. Patients with AML-MDS typically have cytogenetic abnormalities which are associated with MDS, such as monosomy 5 or del(5q), monosomy 7 or del(7q), isochromosome 17p, loss or deletion of chromosomes 16 and 18, gain of chromosomes 1 and 11, and/or complex karyotypes (i.e., three or more numerical and/or structural chromosomal abnormalities). Patients typically have tumor protein 53 (TP53) deletions and/or mutations and a high degree of genomic complexity with an average of 14 aberrations per case [12, 13; see Table 1].

A number of genes have been implicated in the development of AML-MDS including 40S ribosomal protein 14 (RPS14) [14], microribonucleic acid 145/146a (miR-145/46a) [15], enhancer of zeste homolog 2 (EZH2) [16], early growth response protein 1 (EGR1) [17], adenomatosis polyposis coli (APC) [18], and catenin cadherin-associated protein alpha 1 (CTNNA1) [19], and cut-like homeobox 1 (CUX1) [20].

Table 1. Cytogenetic and molecular signatures in S-AML

Disease	Cytogenetics	Molecular signatures
S-AML	Monosomy 5 or del(5q)	Mutations in TP53, DNMT3A, IDH1 and IDH2, ASXL1, SF3B1,
	Monosomy 7 or del(7q)	SRSF2, RUNX1, FLT3, RAS, RPS14, miR-145/46a, EZH2,
	Isochromosome 17p	EGR1, APC, CTNNA1, CUX1
	Loss or deletion of chromosomes 16 and 18	
	Gain of chromosomes 1, 8,11, or 21	
	Complex karyotypes	
	11q23 or 21q22 abnormalities	
	t(9;11), t(19;11) or t(4;11)	

S-AML secondary acute myeloid leukemia, *TET2* ten-eleven translocation, *DNMT3A* deoxyribonucleic acid (cytosine-5)-methyltransferase 3A, *IDH* isocitrate dehydrogenase, *SF3B1* splicing factor 3B subunit 1, *ASXL1* additional sex-comb like-1, *RUNX1* runt-related transcription factor 1, *SRSF2* serine/arginine-rich splicing factor, *TP53* tumor protein p53, *FLT3* fms-related tyrosine kinase 3, *RAS* rat sarcoma, *RPS14* 40S ribosomal protein, *miR-145/46a* micro-ribonucleic acid 145/146a, *EZH2* enhancer of zeste homolog 2, *EGR1* early growth response protein 1, *APC* adenomatosis polyposis coli, *CTNNA1* catenin cadherin-associated protein alpha 1, *CUX1* cut-like homeobox 1

T-AML

The diagnosis of t-AML is made when AML occurs in a patient with prior exposure to cytotoxic agents. The risk of developing t-AML has been estimated to range from 8 to 12 % within 20 years after the diagnosis of a first cancer [21]. It is also possible for a patient to develop t-AML after treatment for a de novo myeloid neoplasm [22, 23]. In these rare circumstances, cytogenetic and immunophenotype evaluation at relapse is compared to that at initial diagnosis. The emergence of a distinctly different karyotype suggests a t-AML rather than recurrence of the original leukemic clone. The incidence of t-AML among patients treated with cytotoxic agents varies according to the underlying disease, specific agents used, timing of exposure, and dose [24]. The most common underlying diseases among patients with t-AML are Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), solid tumors, autoimmune diseases, renal transplant, and autologous hematopoietic cell transplantation (HCT) [25, 26]. Compared to those who receive only one treatment modality, patients that are exposed to both chemotherapy and radiation are at an increased risk for t-AML [27]. Larger doses of chemotherapy and a larger portal of radiation that includes active marrow pose an even greater risk [28]. Cytotoxic agents that have been implicated in t-AML include alkylating agents (i.e., melphalan, cyclophosphamide), topoisomerase II inhibitors (i.e., etoposide, doxorubicin), antimetabolities (i.e., mycophenolate, fludarabine), antitubulin agents (i.e., vincristine, docetaxel), ionizing radiation therapy, and certain environmental agents (i.e., solvents, insecticides; see Table 2).

The most common type of t-AML results from the exposure of patients to alkylating agents or radiation therapy and typically presents after a latency period of approximately 5 to 7 years [22–29]. This latency period suggests that multiple mutational events are involved in the development of the malignant phenotype [30]. Genetic polymorphisms of a number of drug-metabolizing enzymes, such as glutathione S-transferases (GST) and

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Table 2. Agents implicated in T-AML

Class	Examples
Alkylating agents	Melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, procarbazine, carmustine, mitomycin C, thioTEPA, lomustine, bendamustine
Topoisomerase II inhibitors	Etoposide, teniposide, doxorubicin, daunorubicin, mitoxantrone, epirubicin, amsacrine, and actinomycin
Antimetabolites	Thiopurines, mycophenolate, and fludarabine
Anti-tubulin agents	Vincristine, vinblastine, vindesine, paclitaxel, and docetaxel
Ionizing radiation therapy	Large fields that include the bone marrow
Insecticides, solvents	Benzene
Other	Hydroxyurea, L-asparaginase, radioisotopes, and hematopoietic growth factors

T-AML treatment-related acute myeloid leukemia

NAD(P)H/quinone oxidoreductase 1 (NQO1), may alter the risk of t-AML [31–33]. Most of the patients with t-AML and exposure to alkylating agents present with pancytopenia and trilineage dysplasia (MDS-like picture), complex chromosomal abnormalities, and monosomies (–5 or –7). Meanwhile, ionizing radiation damages deoxyribonucleic acid (DNA) by inducing double-strand breaks causing mutations, deletions, or translocations required for hematopoietic stem cell transformation [34, 35]. T-AML resulting from the exposure to topoisomerase II inhibitors has a considerably shorter latency period of 1 to 3 years and most often presents with overt leukemia, as opposed to a more indolent MDS picture [36–43]. Patients commonly have cytogenetic alterations including 11q23 or 21q22 abnormalities and balanced translocations such as t(9;11), t(19;11), or t(4;11) [43]. Patients with t-AML secondary to solvent and/or insecticide exposure commonly have clonal chromosomal abnormalities (92 %), including –5/del(5q), –7/del(7q), +8, or +21, and commonly have rat sarcoma (RAS) mutations [44]. Genetic polymorphisms in the microsomal epoxide hydrolase (HYL1), an enzyme involved in benzene metabolism, have been implicated in t-AML [45]. Patients who develop t-AML after autologous HCT are thought to have had accelerated telomere loss with subsequent genetic instability [46, 47].

Disease Pathogenesis

S-AML is characterized by clonal hematopoiesis and is made up of leukemic cells of different subtypes at various stages of maturation that are maintained by a pool of self-renewing malignant cells [48, 49•]. Two models have been proposed to explain s-AML heterogeneity: (1) any cell type, from primitive multipotent stem cell to lineage-committed progenitor cell, is susceptible to leukemic transformation, resulting in the expansion of abnormal cells that exhibit different stages of differentiation; and (2) mutations responsible for leukemic transformation and progression occur only in primitive multipotent

stem cells, with disease heterogeneity resulting from a variable ability of these primitive stem cells to differentiate and acquire specific phenotypic lineage markers [50, 51]. The "two-hit hypothesis" of leukemogenesis implies that AML is the consequence of at least two mutations, one conferring a proliferative advantage (class I mutations) and another impairing hematopoietic differentiation (class II mutations) [52].

Risk Stratification

Similar to patients with de novo AML, those with s-AML are risk-stratified according to the presence or absence of particular genetic and chromosomal signatures [53–56]. However, unlike de novo AML, there is less evidence to suggest that these genetic signatures are predictive in determining the likelihood of obtaining a complete response with induction chemotherapy. While certain gene mutations, such as fms-related tyrosine kinase 3 internal tandem duplications (FLT3-ITD), CCAAT/enhancer binding protein alpha (CEBPA), and nucleophosmin (NPM1), are routinely incorporated into the risk stratification of de novo AML, there is a paucity of data regarding the incidence of these gene mutations in s-AML. In addition, the majority of data regarding gene mutations in de novo AML is derived from patients with normal karyotypes, which only comprise a small fraction of s-AML.

Genetic Abnormalities

While many genetic mutations have been identified to carry prognostic weight in patients with MDS [57], the significance of these mutations in AML-MDS has yet to be defined. Mutations of ten-eleven translocation (TET2; 15 %) have been shown to portend a favorable prognosis, while mutations in deoxyribonucleic acid (cytosine-5)-methyltransferase 3A (DNMT3A; 8–13 %), isocitrate dehydrogenase (i.e., IDH1 and IDH2), additional sex-comb like-1' (ASXL1; 10–20 % of MDS), splicing factor 3B subunit 1 (SF3B1 gene, 20 % of MDS), serine/arginine-rich splicing factor (SRSF2; 12–15 % of MDS), RUNX1 transcriptional core-binding factor (7–15 %), TP53 tumor suppressor gene (10–20 %), and FLT3 have all been found to be associated with a worse prognosis [58–68].

Chromosomal Abnormalities

Among patients with s-AML, those with favorable cytogenetics have a longer median overall survival than those with normal or unfavorable karyotypes. However, the outcomes among patients with s-AML with favorable cytogenetics are still worse than those with de novo AML in the same cytogenetic risk group [69], perhaps due to other patient-related unfavorable factors in those with s-AML, and small numbers of s-AML patients reported in the literature. Favorable cytogenetics include t(8;21), inv(16), and t(15;17), whereas intermediate cytogenetics include a normal karyotype, t(9;11) and other abnormalities not described as favorable or unfavorable. Unfavorable cytogenetics, more commonly seen in patients with s-AML compared to their de novo AML counterparts, include 3q21q26 abnormalities, del 5q, del 7q, t(6;9), other 11q23 abnormalities, 12p

abnormalities, 17p abnormalities, monosomies 5 or 7, trisomies 8 or 13, and complex aberrant karyotypes [55, 70].

Treatment

When determining the optimal treatment strategy for s-AML, several factors must be taken into account (see Fig. 1). These factors include patient's age, comorbidities, performance status (PS), AML karyotype, and persistence of the primary malignant disease. Patients who are younger, have limited comorbidities, and are fully ambulatory will be more likely to tolerate induction chemotherapy and warrant a more aggressive treatment approach. Meanwhile, patients who are older, have significant comorbidities, and have a poor performance status are at a high risk of dying during induction chemotherapy and may therefore be better served by either less intensive therapy or supportive, symptom-directed care [69]. For those who achieve complete remission, karyotype should guide choice of postremission therapy given that those with favorable karyotype can enjoy long-term remissions with chemotherapy alone for consolidation, and those without favorable karyotypes should be referred for allogeneic transplantation in first complete remission.

While a substantial percentage of patients with s-AML will attain a complete remission (CR) with induction chemotherapy, median survival remains between 6 and 10 months with current treatment approaches [56]. Only about 10 % of patients with s-AML attain long-term survival after the administration of postremission chemotherapy, and those who attain long-term survival are generally only those with favorable or intermediate risk disease [56]. Postremission therapy aims to destroy leukemia cells that survive induction chemotherapy and are undetectable by conventional studies. There are two generally accepted options for postremission therapy: consolidation chemotherapy or allogeneic HCT. Consolidation chemotherapy is less intensive and has a lower early mortality rate, but allogeneic HCT provides a potential graft-versus-tumor effect that may decrease relapse rates and can offer cure to well-selected patients [71]. Allogeneic HCT in s-AML tends to be complicated by high rates of treatment-related toxicity, as patients are typically older, heavily pretreated, and have multiple comorbidities. However, a subset of patients with s-AML may be able to undergo HCT after reduced intensity conditioning regimens [72]. In an effort to shorten the duration of neutropenia and minimize infectious complications among patients, colony-stimulating factors (i.e., GM-CSF, G-CSF) have been tested as an adjunct to intensive chemotherapy. Despite promising early phase studies, larger later phase studies have produced mainly disappointing results [73–78].

Cytogenetic signatures can provide insight on an ideal treatment strategy for s-AML patients who are not excluded from treatment based on age, comorbidities, or PS. Patients with s-AML harboring the infrequently seen favorable karyotypes such as inv(16), t(16;16), and t(8;21) are likely to obtain a complete remission with conventional induction chemotherapy with a combination of anthracycline and cytarabine [56, 79–81]. These patients may achieve long-term survival after consolidation therapy. Similar to de novo acute promyelocytic leukemia (APL), therapy-related APL remains a highly curable disease with risk-adapted therapy [82, 83]. A retrospective analysis of 121 patients with s-AML
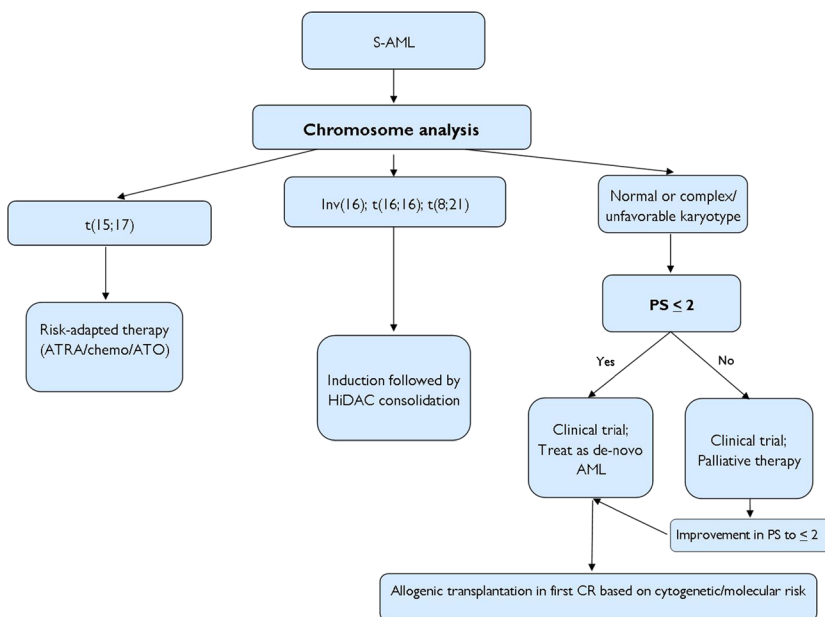
Fig. 1. Treatment algorithm for S-AML. *S-aml* secondary acute myeloid leukemia. *ATRA* all-trans-retinoic acid. *ASO* arsenic trioxide. *PS* performance status. *AML* acute myeloid leukemia. *CR* complete response. *HiDAC* high-dose cytarabine. *Inv* chromosome inversion. *t* chromosome translocation.

treated with conventional induction chemotherapy reported a median overall survival of 27 months in patients who had inv(16), t(8;21), or t(15;17) [80]. The rate of survival at 5 years for 13 patients with t-AML with inv(16) was 62 % compared with 78 % for those with de novo AML with inv(16) [84]. An international workshop analysis of 39 patients with t-AML and inv(16) treated with induction chemotherapy reported a complete remission rate of 85 % [81]. Another international workshop analysis of patients with 21q22 balanced translocations reported median overall survival of 19 months for those with t(8;21) compared to 7 months for those without t(8;21) [85].

Patients with an intermediate risk karyotype comprise 25 % of patients with s-AML. There is limited evidence to guide therapy, but these patients appear to have a greater frequency of relapse after conventional induction therapy and consolidation [80, 84, 86, 87, 88•]. For most patients with s-AML and intermediate risk karyotype, the treatment most likely to offer a cure is standard induction chemotherapy followed by an allogeneic HCT (if a human leukocyte antigen (HLA) matched donor is available) rather than consolidation chemotherapy alone. However, chronic and cumulative toxicities from prior chemo-radiation have an impact on the ability to perform HCT and adversely affect survival. Therefore, due to patient- and disease-related factors (e.g., age, comorbidities, accumulation of resistant leukemia clones), earlier mortality associated with regimen-related toxicity is more common after HCT for therapy-related leukemia than for de novo AML. The center for international bone marrow transplant research (CIBMTR) carried out a retrospective study of 868 patients who underwent allogeneic transplantation for the treatment of therapy-related AML and MDS, among them 545 had t-AML. Five-year treatment-related mortality was 48 %, and 5-year overall survival was 22 % [88•]. Factors associated with worse outcomes included age older than 35 years, t-AML not in remission or advanced t-MDS, poor-risk cytogenetics, and donor other than an HLA-identical sibling or a partially/well-matched unrelated donor. In that study, the

number of risk factors could predict survival, with the best posttransplantation survival, comparable to that of de novo AML patients, for the group with zero risk factors and dismal outcomes for those with 3–4 risk factors.

S-AML patients with an unfavorable karyotype (48 %) do poorly with all currently known treatment options. In patients of relatively young age (i.e., less than 40 years), conventional induction chemotherapy followed by early allogeneic hematopoietic cell transplantation is typically strongly considered. Older patients are encouraged to enroll in a clinical trial of an investigational therapy. Some patients choose only supportive care, which includes the use of red blood cell (RBC) and platelet transfusions, antibiotics, and control of leukocytosis with agents such as hydroxyurea.

Patients may elect less intensive chemotherapy such as DNA hypomethylating agents (i.e., azacitidine, decitabine), which are pyrimidine nucleoside cytidine analogs and are commonly used for the treatment of MDS. Although the US Food and Drug Administration (FDA) has not approved these agents for the treatment of AML, clinical trials have demonstrated the ability of these agents to induce remissions and potentially prolong survival [89, 90•, 91–94]. A phase III study in high-risk MDS randomly assigned patients to therapy with azacitidine versus conventional care (i.e., best supportive care, low-dose cytarabine, or AML induction chemotherapy) and found a survival benefit among patients with AML who received azacitabine [93]. In another phase III study, 45 patients with AML-MDS were randomly assigned therapy with conventional care or azacitidine [92]. The overall response rate (ORR) in patients receiving azacitabine was 60 % and patients reported improvements in physical function, symptoms, and psychological state [91–93]. A phase III trial of older adults with s-AML who had intermediate and adverse cytogenetics were randomly assigned to decitabine or conventional care [94]. Decitabine was associated with a higher rate of complete response (18 vs 8 %), a trend toward increased median overall survival (7.7 vs 5.0 months) that did not reach statistical significance, and higher rates of febrile neutropenia (24 vs 14 %). An additional phase II study demonstrated similar response rate, median survival, and rates of adverse effects [95].

Prognosis

The prognosis of patients with s-AML is heterogeneous and dependent on many different factors including patient-related factors (e.g., age, performance status, comorbidities) and disease-related factors. The secondary nature of the disease is not in and of itself considered an adverse prognostic factor. Instead, patients who present with s-AML tend to have more adverse outcomes because of the increased likelihood of older age and increased frailty, as well as an increased incidence of numerous chromosomal and molecular abnormalities in this population [96, 97; Table 3]. The most powerful prognostic factors in terms of overall survival (OS) are cytogenetic and molecular signatures. The European Leukemia Net (ELN) classification of de novo AML is a well-validated tool that integrates age, cytogenetics, and molecular features and divides patients into four prognostic risk groups: (1) favorable risk (young adult median OS= 11.5 years, older adults median OS=1.6 years); (2) intermediate-I risk (young adult median OS=1.2 years, older adult median OS=0.9 years); (3)

Table 3. Prognostic factors in acute myeloid leukemia (AML)

Categories	Favorable	Unfavorable
Age	<60	>60
ECOG PS	≤2	>2
Cytogenetics	1) t(8;21)	1) del (5q)
	2) inv(16)/t(16;16)	2) add (5q)
	3) t(15;17)	3) del (7q)
		4) add (7q)
		5) monosomies 5 or 7
		6) inv(3)
		7) t(3;3)(q21;q26)
		8) t(6;11)
		9) t(10;11)
		10) t(9;22)
		11) 17p abnormalities or monosomy 17
		12) Complex aberrant karyotypes
		13) 11q23 abnormalities excluding t(9;11) and t(11;19)
		14) 3q abnormalities excluding t(3;5)
Molecular Signatures*	1) NPM1 mutation without *FLT3*-ITD (normal karyotype)	1) FLT3/ITD mutation
	2) CEBPA mutation	2) MLL partial tandem duplication
		3) BAALC overexpression
		4) IDH1/IDH2 mutations

*Not validated in s-AML
ECOG PS Eastern cooperative oncology group performance status, *FLT3/ITD* FMS-like tyrosine kinase 3 gene producing internal transmembrane duplications, *NPM1* nucleophosmin-1, *MLL* mixed lineage leukemia, *BAALC* brain and acute leukemia, cytoplasmic, *IDH1/2* isocitrate dehydrogenase 1 and 2, *Complex cytogenetics* ≥4 clonal chromosomal abnormalities, *CEBPA* CCAAT/enhancer binding protein alpha, *Del* chromosome deletion, *Add* chromosome addition, *Inv* chromosome inversion, *t* chromosome translocation

intermediate-II risk (young adult median OS=2.1 years, older adult median OS=0.9 years); and (4) unfavorable risk (young adult median OS=0.8 years, older adult median OS=0.5 years) [98•]. However, due to the few numbers of patients with s-AML in studies validating the ELN classification, caution is advised when extrapolating those results to s-AML [99]. A comparative analysis that included 93 patients with s-AML and 1091 patients with de novo AML treated with AML induction therapy found that patients with t-AML had a significantly shorter median OS after treatment (10 vs 15 months), which was seen even after correcting for some cytogenetic risk groups, but not all of the validated AML prognostic factors [84]. The median OS times for patients with s-AML with favorable, intermediate, and unfavorable cytogenetics were 27, 13, and 6 months, respectively [80]. A study from the University of Chicago, including 74 patients with s-AML found a median OS of approximately 7 to 9 months, which varied with karyotype [24].

Future Directions

Several chemotherapeutic agents have been tested in clinical trials over the past several years, but none of them have proven to improve the OS for patients with s-AML. Clofarabine, a second-generation purine nucleoside analog, showed

promise in early phase trials, but failed to improve survival in a subsequent phase III trial [99–101]. The histone deacetylase inhibitor vorinostat, the proteasome inhibitor bortezomib, and the immunomodulatory agent lenalidomide all produced promising results in early phase studies as both single agents and as part of combination systemic chemotherapy, but all failed to improve survival in later phase studies [102–106]. Gemtuzumab ozogamicin (GO), a recombinant, humanized anti-CD33 antibody linked to the cytotoxic agent calicheamicin, was initially approved in the USA for patients aged 60 or older with CD33+ AML in first relapse who were not considered candidates for cytotoxic chemotherapy. However, GO was later removed from the market after the results from a subsequent randomized trial failed to confirm its clinical benefit [107–111]. Several phase II studies evaluating oral FLT3 tyrosine kinase inhibitors with or without chemotherapy have demonstrated antileukemic activity, but a survival benefit has yet to be shown [112–117]. Multiple clinical trials of promising targeted agents are ongoing [118].

Conclusion

S-AML has traditionally been considered to be a devastating disease. It affects a vulnerable patient population that includes primarily older adults who have been heavily pretreated and who have multiple comorbidities. A limited understanding regarding disease pathogenesis and tumor heterogeneity combined with the lack of effective treatment options has hampered the overall improvement in patient outcomes. However, with the incorporation of cytogenetics and molecular genetics into patient care and the advancement of s-AML treatment, including improved supportive care, novel chemotherapeutics agents, and nonmyeloablative conditioning regimens as part of allogeneic hematopoietic cell transplantation (HCT), modest gains in the survival and quality of life of patients are beginning to be seen among patients with s-AML.

Compliance with Ethics Guidelines

Conflict of Interest
Simon B. Zeichner and Martha L. Arellano declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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