Secondary Acute Myeloid Leukemia

A Primary Challenge of Diagnosis and Treatment

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KEYWORDS

- Acute myeloid leukemia • Secondary acute myeloid leukemia
- Therapy-related acute myeloid leukemia
- Acute Myeloid Leukemia Caused by an Antecedent Hematologic Disease
- Acute Myeloid Leukemia with Myelodysplastic-Related Changes

KEY POINTS

- Secondary acute myeloid leukemia (sAML) is a unique diagnostic entity with specific clinical and laboratory characteristics.
- sAML independently carries a poor prognosis.
- Challenges to treating the sAML population include high rate of comorbidities in patients and chemorefractory disease.
- Improvement in molecular diagnostics and novel therapies will lead to improved outcomes in this high-risk population.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogenous, aggressive myeloid malignancy. In 2018, an estimated 19,520 new cases and 10,670 deaths occurred in the United States.[1] Although strides have been made in AML treatment using novel therapies and small molecule inhibitors, the 5-year overall survival (OS) is only approximately 27%.[2,3] Contributing to this dismal prognosis is the increasing rates of secondary AML (sAML), which describe a subset of AML that arises from either an antecedent hematologic disorder (AHD) such as myelodysplastic syndrome (MDS), or are related to prior exposure to cytotoxic chemotherapy agents or radiation therapy. The incidence of sAML ranges from 10% to 35% of AML cases.[4,5] This article focuses on the epidemiology, diagnosis, pathogenesis, molecular, and treatment of sAML.

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DIAGNOSIS AND CLASSIFICATION

Secondary AML occurs by 2 separate mechanisms, either through an antecedent hematologic disorder (AHD) or prior chemotherapy or radiation therapy, and the classification of AML has begun to reflect this etiology.[6] In a study evaluating the ontogeny of AML, distinct somatic mutations differentiated AML subtypes between de novo AML, AML-AHD (labeled as s-AML), and therapy-related AML (t-AML).[7] Multiple analyses have been studied to determine the transformational cause for the change from AHD to AML. Clonal evolution in AML is common, with many of the mutations occurring as random events, then acquiring a cooperating mutation leading to proliferation of the malignant clone.[8] In 2008, the World Health Organization (WHO) introduced the diagnosis of AML with myelodysplasia-related changes (AML-MRC), which was later expanded to specific criteria in the 2016 WHO classification system.[6,9] This newer classification requires a prior history of MDS, MDS-associated cytogenetic abnormalities, or multilineage dysplasia, but specifically excludes prior cytotoxic chemotherapy or radiation therapy and entity-defining recurring cytogenetic abnormalities.[10] The classification of AML-MRC has a high frequency of mutations in ASXL1 mutations, and a low rating of NPM1, FLT3, and DNMT3A mutations.[11] Patients with AML-MRC who have either the ASXL1 mutation or TP53 mutations are associated with shorter OS.[12] In a retrospective study of Chinese patients with AML-MRC, patients had significantly shortened complete response (CR) rates, disease-free survival (DFS), and OS compared with AML-NOS patients.[13]

PATHOPHYSIOLOGY

t-AML is defined as AML occurring in patients previously treated with chemotherapy, radiation therapy, or immunosuppressive therapy.[14] The incidence of therapy-related MDS (t-MDS) and t-AML ranges from 0.8% to 6.3% at 20 years, with a marked decrease in incidence after 10 years.[15] The classic teachings associate t-AML with alkylating agents, with a latency period of 5 years, and topoisomerase II inhibitors, with a latency period of 1.5 years.[16,17] Radiation also is associated with t-AML, as demonstrated by an Italian breast cancer study that controlled for chemotherapy treatment regimens.[18] In a large case-controlled study in breast cancer, the risk of AML was far higher in patients receiving alkylating agents alone (relative risk [RR] 10.0) than with radiation alone (RR 2.4), but the combination displayed the highest risk (RR 17.4%).[19]

Unique chromosomal abnormalities frequently occur with t-AML. A large Swedish pooled analysis demonstrated an increase in complex and hypodiploid karyotypes. Furthermore, certain chromosomal abnormalities corresponded with specific treatments, such as 5q- and radiotherapy, monosomy 7 and monosomy 5 with alkylating agents, and t(11q23) and other balanced translocations with topoisomerase II inhibitors.[20,21] Not surprisingly, combination chemoradiation therapy has the highest incidence of t-AML, and a higher frequency of complex karyotype.[22] The prognosis of t-AML depends on these cytogenetic abnormalities.[23]

Molecular studies have also elucidated the pathway of t-AML. Point mutations in AML1 and RAS seem to predispose the patient to progression from t-MDS to AML.[21] However, the most commonly mutated gene in t-AML is TP53, occurring in 37% of t-MDS/t-AML cases compared with 14.5% of de novo MDS/AML cases.[24] It is well established that TP53 is associated with leukemogenesis and complex karyotype, and is associated with poor prognosis.[25,26] One theory of p53 pathogenesis is that a small percentage of patients is predisposed to TP53 selection by possessing mutations as clonal hematopoiesis of indeterminate potential.[27] In a small study

evaluating 22 patients with t-AML, 4 patients had the exact founder mutation at diagnosis that was also present at low frequencies (0.003%–0.7%) in mobilized peripheral leukocytes or bone marrow 3 to 6 years before the development of t-AML; in 2 cases, patients had the founder TP53 mutation prior to initiation of chemotherapy.[28] These data may indicate chemotherapy may not be a direct inducer of TP53 mutations, but rather a selector of the hematopoietic stem cells that possess the clonal age-related p53 mutation promoting expansion.

The remainder of sAML is associated with an AHD. This includes MDS, aplastic anemia, and the myeloproliferative diseases, including chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, and essential thrombocythemia.[29] MDS is a heterogeneous diagnosis; in low-risk MDS with refractory anemia, approximately 2% of cases will transform to AML, while in the subset with excess blasts-2, approximately 40% will progress to AML at 5 years.[30] The transformation process from MDS to AML is slowly being elucidated. In 1 study, whole-genome sequencing demonstrated a clonal evolution with nearly all bone marrow cells in patients with MDS and sAML being clonally derived, with 1 of 11 distinct mutations acquired in addition to the antecedent founder clone.[31] Further studies evaluating the progression from MDS to sAML in paired samples demonstrated that 60% of patients acquired additional mutations (24% cytogenetic, 26% molecular, 11% both) leading to the progression from MDS to sAML.[32] Furthermore, although specific genes are common in the initiation of MDS, such as SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, and STAG2, the addition of progression mutations such as RUNX1, GATA2, and CEBPA are often needed to evade normal cellular differentiation.[7] Other mutations, such as FLT3 and Ras family mutations often become the driver mutation to sAML because of the effect of dysregulation of cellular proliferation.[33] Often these comutations are from different classes of biologic function and create a pattern of functional complementarity.[34]

Further mutational analyses have attempted to clarify the transformation from MDS to sAML. RUNX1 is a common mutation in MDS, but seems to have an increased incidence in sAML.[35] A transcription factor essential for normal hematopoiesis, RUNX1 is seen in high frequency of CMML and MDS cases; RUNX1 mutants in these diagnoses have reduced DNA binding. This low RUNX1 activity correlated with both a higher risk and shorter time to the development of sAML.[36] DNMT3A mutations, typically found in de novo AML with mutations in the arginine on position 882, are also noted in sAML and can be found in the antecedent disorder, but the mutation is more frequently seen in the methyltransferase domain.[37] TET2 mutations, common in de novo MDS, occur more frequently in sAML compared with AML-MRC and did not associate with mutations of NPM1, FLT3, Ras, or WT1. In a multivariate large database analysis, there was noted linearity in the transformation curves from MDS to AML over time when the group was divided by IPSS subsets; this led investigators to hypothesize that duration of MDS may not be of prognostic relevance, but rather the transformation is caused by a single epigenetic or genetic event.[38] This concept of a single event leading to leukemogenesis in sAML patients was also reported by Milosevic and colleagues,[39] who identified 36 recurrent aberrations.

Other secondary causes of AML are uncommon. Myeloproliferative neoplasms (MPNs) have a lower rate of transformation to sAML, and patients with transformation from JAK2 MPN have higher incidence of DNA methylation mutations (most commonly *ETV6*, *NRAS, BCOR, SF3B1, CBL, GATA2, RAD21, KRAS, ABL1* and *PTPN11)* and complex karyotype. TP53 was noted in both MPN-driven and de novo AML; a study evaluating the functional analysis of leukemic transformation in MPN demonstrated frequent acquisition of TP53 mutations.[40,41] Nonmalignancy diagnoses associated

with sAML include chemical exposure such as benzene (odds ratio [OR] 1.77), vinyl chloride (OR 2.81), and other environmental exposures but into pesticides or agricultural chemicals.[42] A study evaluating autoimmune therapy such as azathioprine demonstrated an increase in sMDS/sAML (OR 7.05).[43] Lastly, there is a study suggesting that number of apheresis days prior to autologous stem cell transplantation for lymphoma may be a predictor of the development of sMDS/sMDS, but this may not be a causal effect but rather a predictive one.[44]

EPIDEMIOLOGY AND PROGNOSIS

Multiple studies have tried to elucidate the true incidence and other prognostic factors for s-AML. In a Swedish registry study including 3363 adult patients with AML, 639 (18.7%) had AHD-AML, while 259 (7.7%) had t-AML (**Table 1**).[45] A second population study from Denmark evaluated 3055 unselected patients and noted a frequency of sAML of 19.8% and of t-AML 6.6%.[5] The German-Austrian AMLSG surveyed 2653 AML patients and noted 200 (7.0%) to have t-AML; secondary AML data were not provided.[46] A Czech Republic study evaluated 1516 patients, 328 of whom were diagnosed with s-AML (21.6%), but this study did not differentiate between s-AML and t-AML. Descriptively, the s-AML population was older, had a higher frequency of unfavorable cytogenetics, and were less likely to receive curative therapy.[47]

Age carries a mixed prognosis in s-AML. In the Swedish study, there was not a significant difference in median age between s-AML and de novo AML (73 years vs 71 years); however, there was a significant difference in incidence below age 40.[45] Also, although younger patients tended to do well in de novo AML, survival was poor in s-AML and similar to the elderly patients (158 months vs 7–14 months in patients < 55). In the Czech study, the median age of s-AML patients was 5 years older, with a higher proportion of patients over the age of 60.[47] In the Danish study, patients under 60 had an increased relative risk for death in s-AML and t-AML, whereas in older patients, s-AML and t-AML had no impact on survival.[5] One further transplant study in sAML and MDS revealed an increase in significant complications and late treatment-related mortality for patients aged 65 years and older versus patients younger than 45 years of age.[48]

Response to chemotherapy and OS was heavily impacted by s-AML versus de novo AML. In the Czech study, the complete remission was achieved in only 48.9% of patients who received curative therapy compared with 74.6% of de novo AML cases ($P<.001$). Differences in OS were also noted in the groups achieving CR, with the s-AML group having a median OS of 14.1 months compared with 37.4 months in de novo AML.[47] The Danish study created subsets of s-AML from MDS (MDS-sAML), s-AML from other AHD (non-MDS-AML), and t-AML. All 3 categories had a worsened odds ratio to achieve a CR (MDS-sAML 0.47, non-MDS-sAML 0.39, t-AML 0.51).[5] The data from the Swedish study mimicked the aforementioned studies, with CR rates of 72% in de novo AML, but only 54% of t-AML and 39% in AHD-AML. A multivariable Cox regression analysis showed both AHD-AML and t-AML to be independently associated with poor survival (HR 1.51 and 1.72, respectively).[45]

Other studies present a retrospective report of their s-AML patients. The Duke University group evaluated 96 patients with AML treated with induction chemotherapy, and demonstrated a CR rate of 73%; patients with t-AML had a higher response rate (82%) compared with s-AML (62%). However, long-term prognosis was still poor, with an event free survival (EFS) of 8 months and OS of 13.6 months.[49] A second report from MD Anderson detailed s-AML strictly defined as prior MDS, MPN, or aplastic anemia, with at least 1 treatment for that diagnosis. CR rates and

Table 1
Characteristics of secondary acute myeloid leukemia

Author	N	Age	% Secondary Acute Myeloid Leukemia	Complete Response Rate with Intensive Chemotherapy	Survival	Other Data
Hulegårdh et al,[45] 2015	3363	17–98	18.7% AHD-AML 7.7% t-AML	72% de novo 39% AHD-AML 54% t-AML	Independent risk factor for poor survival AHD-AML HR 1.51 t-AML HR 1.72	Worse prognosis in younger population (<55) De novo: 158 mo AHD-AML: 7 mo t-AML: 14 mo
Szotkowski et al,[47] 2010	1516	19–92	21.6% sAML	74.6% de novo 48.9% sAML	Median OS: De novo: 18.2 mo sAML: 8.2 mo	Age and cytogenetics as independent risk factors for OS
Østgård et al,[5] 2015	3055	15–87	19.8% sAML (AHD) 6.6% t-AML	75% de novo 59% MDS-sAML 61% t-AML 54% non-MDS-sAML	1 y/3 y OS: de novo: 65%/39% MDS-sAML: 56%/25% t-AML: 45%/24% Non-MDS-sAML: 31%/11%	Non-MDS-AML as inferior survival across all age and cytogenetic risk groups
Boddu et al,[51] 2017	931	60–75	100%	46% with IC 45% with Vyxeos 36% with HMA 43% with LDAC	Median OS: IC: 5.4 mo Vyxeos: 7.6 mo HMA: 6.7 mo LDAC: 7.1 mo	Lower-intensity regimens in this older population had improved OS
Rizzieri et al,[49] 2009	96	22–82	100%	58% with IC	1 y OS: 51%	Median DFS of 11 mo.
Bertoli et al,[52] 2019	218	60–75	100%	CR/CRi 69.4% IC CR/CRi 15% HMA	Median OS: 11 mo IC 11 mo HMA	3 y/5 y OS: 21% and 17% IC 15% and 2% HMA

Abbreviations: AHD, antecedent hematologic disease; HMA, hypomethylating agent; t-AML, therapy-related AML.

8-week mortality rates were 32% and 27%, respectively in patients younger than 60 years and 24% and 19% respectively in patients aged 60 years and older.[50] In a companion study, the same group evaluated s-AML in older patients stratified by intensive chemotherapy (IC), hypomethylating-based therapy (HMA), low-dose cytarabine-based regimens (LDAC), Vyxeos (CPX-351), and investigational agents. CR rates were higher in the IC, Vyxeos, and LDAC arms compared with HMA, but the lower-intensity regimens (HMA and LDAC) had superior OS compared with IC (6.9 months vs 5.4 months).[51] A French study presented their experience with s-AML cases receiving either IC or HMA. The IC group achieved a CR rate of 69% and OS of 11 months, while the HMA group achieved a CR rate of 15%, but an identical median OS of 11 months. However, different 3- and 5-year OS rates were noted, with the IC group demonstrating 21% and 17% ,respectively compared with 15% and 2% in the HMA group.[52]

The German Study Alliance Leukemia (SAL) evaluated patients in the AML96 trial with sAML. This study found absolute platelet count and NPM1 gene mutation status as prognostic factors.[53] These risk factors were added to known risk factors of age and karyotype. This created 3 score groups that stratified 2-year OS and EFS of 53% and 44%, respectively, in the low-risk group, 21% and 12%, respectively, in the intermediate risk group, and 7% and 3%, respectively, in the high-risk group.

TREATMENT

Unfortunately, there are few prospective clinical trials that solely evaluate sAML, as it is a small subset of AML; often these patients are excluded from individual trials. Further complicating treatment strategies is that these patients have often received prior treatment for an antecedent hematologic disorder, exposing patients to commonly used agents for AML treatment (ie, hypomethylating agents in MDS) or increasing comorbidities by chemotherapies used in treating previous solid tumors.[16] Although recent advances in novel therapies created more therapeutic opportunities, these options have not been proven in sAML patients; therefore, further studies are needed in this unmet population.

Standard Therapy

For almost 50 years, the standard of care for fit AML patient was 7 + 3 chemotherapy, combining 7 days of cytarabine with 3 days of anthracycline.[54] Subsequent large randomized studies have attempted to tailor the dosing to maximize efficacy, but overall the response for all AML patients ranges from 54% to 82%.[55–58] The subsets of secondary AML patients were not part of any planned analyses, but some data were included in individual studies. In a study in patients over the age of 60 comparing daunorubicin at 45 mg/m^2 with 90 mg/m^2, the sAML patients, particularly with prior MDS, had a lower likelihood of achieving a complete remission (OR 0.44).[57] The British AML17 trial, which compared double induction daunorubicin 90 mg/m^2 with 60 mg/m^2 therapy did not demonstrate any difference in outcome from treatments in the de novo, secondary, or MDS groups.[58] A Korean study also evaluating daunorubicin at 45 mg/m^2 with 90 mg/m^2 had a small subset of sAML (4.4%) and noted a trend toward lower CR rates (de novo 78.1% vs 58.8%, P=.63).[55]

Other Traditional Chemotherapies

CPX-351 (Vyxeos) is a liposomal-encapsulated cytarabine:daunorubicin mixture at a 5:1 M ration, which effectively translates to 1 unit of CPX-351 containing 1 mg of cytarabine and 0.44 mg of daunorubicin. This novel delivery system maintains the 5:1 ratio,

and the drug's synergistic effects and maximizes drug delivery to leukemic cells.[59] After a phase I dose escalation trial demonstrated safety,[60] The phase II study included older AML patients and randomized them to CPX-351 versus 7 + 3. CPX-351 yielded a higher CR rate (66.7% vs 51.2%) with no difference in EFS and OS. However, a planned subset analysis of sAML patients demonstrated improved although not statistically significant response rates (57.6% vs31.6%, P = 0/06) and prolongation of OS (HR = 0.46, P=.01).[61]

These promising results led to a phase III trial specific to untreated sAML.[62] The eligibility criteria included patients aged 60 to 75 years with either newly diagnosed t-AML, AML with antecedent MDS or CMML, or de novo AML with MDS-related cytogenetic abnormalities based on the 2008 WHO criteria. Patients who had previously received HMA were eligible, and the primary end point was survival. Patients were randomized to receive either CPX-351 at 100u/m^2 or standard induction with cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2.

The results of this sAML trial were practice changing. Three hundred nine patients were randomized, and full analysis demonstrated in improved OS with CPX-351 compared with standard induction (9.56 months vs 5.95 months). Kaplan-Meier estimates favored the CPX-351 group (1-year OS 41.5% vs 27.6% and 2-year OS 31.1% vs 12.3%). The CR + CR rate with incomplete count recovery (CRi) also was higher in the CPX-351 arm compared with an underperforming 7 + 3 (47.7% vs 33.3%, P=.04). Rates of adverse events were similar between the 2 groups. Multiple subgroup analyses were evaluated in the study, with the survival benefit of CPX-351 consistent across all age groups, but nonsignificant differences noted in patients with MDS with prior HMA exposure (CPX-351 5.65 vs 7 + 3 7.32 months), de novo AML with MDS karyotype (10.09 vs 7.36 months), unfavorable cytogenetics (6.6 vs 5.16 months) FLT3 mutation (10.25 vs 4.6 months), and all prior HMA exposure (5.65 vs 5.9 months). Further subset analysis evaluated survival following allogeneic transplant and demonstrated that of the 91 patients transplanted, there was a higher 100-day mortality in the 7 + 3 group (20.5% vs 9.6%) and a markedly better OS in the CPX-351 arm (HR 0.46, P=.0046). These data led to US Food and Drug Administration (FDA) approval of CPX-351 in patients over 18 years of age with t-AML or AML-MRC.

A smaller study evaluated the use of CPX-351 at low doses 32 or 64 U/m^2 versus the standard 101 U/m^2 in a phase II study.[63] The sAML patients accounted for 55.3% of all patients. The 64 U/m^2 arm was stopped early because of 4 early deaths in the first 10 patients, and the remaining patients were treated at the 32 U/m^2 dose. Unfortunately, the ORR was only 26.3%, with a median OS of 3 months; the death rate within 28 days was 28.9%.

Other studies have attempted to determine a better conventional chemotherapy treatment for sAML. One study examined continuous fludarabine with cytarabine and G-CSF (FLAG) in elderly patients with AML secondary to MDS. The CR rate was 67% with an OS of 9 months and 5-year survival of 15%.[64] The FOSSIL study retrospectively analyzed patients with sAML who received either FLAG or 7 + 3; these data showed FLAG had a higher response rate defined as CR + CRi + morphologic leukemia-free survival (MLFS) of 70% versus 48% but no difference in OS.[65] A further study by the EORTC-GIMEMA AML-12 trial evaluated high-dose cytarabine in induction, with patients age 15 to 60 years receiving daunorubicin, etoposide and either cytarabine (100 mg/m^2 daily) for 10 days or high-dose cytarabine (3000 mg/m^2) twice daily on days 1, 3, 5, and 7. The high-dose cytarabine group achieved higher CR rates, particularly in patients under the age of 46 years, and subgroup analysis demonstrated an improvement in the CR rate in patients with sAML for younger (OR 5.99) and older (OR 3.75) patients.[66] Although intensive chemotherapy has induced some improved

responses by changing agents, a retrospective analysis in 299 patients with high-risk MDS and sAML demonstrated that patients who received intensive chemotherapy did not have an improvement in overall survival compared with those not undergoing intensive chemotherapy.[67]

Hypomethylating Agents

Hypomethylating agents are often the backbone of sAML treatment due the simple fact that these patients are often older, have comorbidities, and are not eligible for induction chemotherapy. Treatment with the hypomethylating agents, decitabine and azacitidine, is effective in MDS and sAML patients, because these diseases have an abundance of DNA methylation.[68] In the AZA-001 study, which was a phase III study comparing azacitidine to conventional care, 34% of the patients were classified as having refractory anemia with excess blasts in transformation (RAEBT), now defined as AML. Although there were not subset data for these RAEBT patients, the study showed an overall improvement in the azacitidine arm with regards to OS compared with best supportive care (HR 0.58, *P*-=.0045), and time to transformation to AML across all subgroups (HR 0.50, *P*<.0001).[69] A French retrospective study evaluated azacitidine compared with IC in sAML and demonstrated no difference in OS (azacitidine 10.8 months, IC 9.6 months, *P*=.899). Subgroup analysis showed that in patients who had not received treatment in 1.6 years for their antecedent disease, the IC arm had a lower risk of death compared with azacitidine (HR 0.61, 95% confidence interval (CI) 0.38–0.99 at 1.6 years).[70]

Decitabine at the standard 5-day dose was also evaluated in a randomized phase III trial versus best supportive care or LDAC in older AML patients.[71] This study, which had 39.3% of participants defined as sAML, demonstrated a nonsignificant difference in median OS with decitabine, with HR in sAML also nonsignificant (0.92; 0.66–1.29).[71] Decitabine has recently undertaken a much more prominent role it the treatment of p53 AML. In a paper by Welch and colleagues,[72] 21 of 21 patients with TP53 mutations responded to 10-day decitabine at a dose of 20 mg/m^2 with a median response duration of 12.7 months. Although this paper did not specifically subset for AHD or tAML, the TP53 mutation alone is highly linked to these diagnoses.[7]

Novel Agents

Gemtuzumab ozogamicin (GO) is a humanized antibody-drug conjugate that binds an anti-CD33 immunoglobulin G_4 antibody to the DNA toxin calicheamicin. It received accelerated FDA approval in 2000 for CD33 + AML, but was voluntarily withdrawn in June 2010 after a postmarketing study demonstrated a higher induction mortality with no improvement in CR or RFS.[73] The drug was then reapproved in September 2017 based on new safety data with a lower fractionated dosing regimen.[74] This study showed an improvement at 2 years in EFS (40.8% vs 17.1%), OS (53.2% vs 41.9%) and RFS (50.3% vs 22.7%). In subset analysis, it appears that the favorable or intermediate-risk cytogenetic groups had the best responses. The study was not analyzed for sAML.

Further studies analyzed which patients would benefit most from the addition of gemtuzumab.[75] Again, results from this study favored the favorable cytogenetic group, with a trend for benefit in the intermediate-risk group, and no benefit for the poor-risk group. A further study specifically evaluated older patients from age 61 to 75 years, including an sAML subset (29.7%).[76] No subgroup had benefit from the addition of GO with regards to CR or OS, although a nonsignificant trend in the sAML for benefit was noted. A smaller trial attempted a different strategy by combining GO with arsenic trioxide in patients with sAML or MDS. This phase II study yielded a response in 30% of patients, with a median OS of 9.7 months.[77]

B-cell leukemia/lymphoma-2 (BCL2) is an antiapoptotic protein that promotes survival of leukemic blast through regulation of the mitochondrial apoptotic pathway. Sensitizer BCL-2 homology 3 (BH3) proteins are antagonists of these antiapoptotic proteins and therefore promote apoptosis via mitochondrial outer membrane permeabilization.[78] Venetoclax, an oral small molecule BCL-2 inhibitor, demonstrated on-target BCL-2 inhibition by BH3 profiling and an overall response rate of 19% in a single agent trial in very advanced AML.[79] Venetoclax was combined with HMA in a phase IB dose escalation and expansion study in an elderly, unfit population. This study resulted in a CR + CRi rate of 73% at that selected dose of venetoclax 400 mg daily. Although not a planned subset, the sAML population accounted for 25% of the study population and had the same CR + CRi rate as the de novo population, but potentially a longer duration of response (not reached [NR] vs 9.4 months) and OS (NR vs 12.5 months). These data led to the FDA approval of venetoclax in combination with HMA for the treatment of newly diagnosed AML in adults age 75 or older or who have comorbidities that preclude the use of intensive induction chemotherapy.

A second phase IB/II study combined venetoclax with low-dose cytarabine in a similar untreated AML population ineligible for intensive chemotherapy.[80] The CR + CRi rate with this regimen was 54%, with a recommended phase II dose of venetoclax at 600 mg daily. The sAML population comprised 49% of the study, with the CR + CRi rate markedly worse in the sAML population compared with the de novo population (35% vs 71%).

Bone Marrow Transplant Studies

It is common knowledge that sAML patients are rarely if ever cured with conventional chemotherapy, and therefore data from consolidative bone marrow or stem cell transplants (BMT) are imperative when discussing long-term prognosis. Early studies demonstrated a 2-year OS, EFS, relapse rate, and transplant-related mortality of 30%, 28%, 42%, and 49%, respectively.[81] More recent retrospective studies often combine MDS and sAML patients; 1 study demonstrates a 4-year estimate for OS of 31%, with multivariate analysis showing reduced intensity conditioning (RIC) transplants and advanced stage associated with increased relapse.[82] A second study showed OS of 37% at 1 year and 22% at 5 years, with multivariate analysis demonstrating age greater than 35, poor risk cytogenetics, t-AML or advanced t-MDS, and donor other than HLA identical sibling or partially or well-matched unrelated donor was associated with worsened DFS and OS.[83] A large retrospective study by the Acute Leukemia Working Party of the European Society for Blood and Bone Marrow Transplantation evaluated 4997 patients with sAML.[84] Two-year OS was 44.5%, and patients receiving myeloablative regimens had decreased relapse and higher nonrelapse mortality, but no difference in OS from RIC regimens. Allogeneic transplant was associated with improved survival compared with no transplant in sAML patients, particularly those who had failed hypomethylating treatment.[85] However, despite the data establishing the poor prognosis of sAML, 2 separate retrospective studies demonstrated comparable outcomes between sAML and de novo AML in first remission.[86,87]

Further transplant variables may determine the outcome of sAML patients. Another European study by the Acute Leukemia Working Party evaluation transplants in sAML demonstrated myeloablative transplants yielded lower relapse rates and improved overall survival compared with RIC tranplants.[88] Furthermore, source of stems cells may also play a role in outcome; a retrospective study in sAML patients showed umbilical cord transplants were associated with higher risk of grade II-IV acute graft-versus-host disease compared with haploidentical transplants with no difference

chronic GVHD, relapse rate, nonrelapse mortality, LFS, and OS.[89] Unfortunately, BMT is not always curative, and patients with sAML who relapse after transplant have a median survival rate of 4.7 months and a 2-year survival rate of only 17.7%.[90]

SUMMARY

The treatment of sAML has evolved from the singular option of standard 7 + 3 induction chemotherapy. Although the discovery of novel inhibitors such as the FLT3 inhibitors of IDH inhibitors has provided targeted therapy for all patients with AML, these agents do not provide the therapeutic boost to sAML patients, as these mutations are infrequent. However, advances in chemotherapy such as Vyxeos (liposomal daunorubicin:cytarabine) have proven overall benefit in sAML over 7 + 3 in fit candidates, and the addition of venetoclax to HMA in the unfit population seems to benefit both de novo and sAML. Furthermore, the treatment of prolonged decitabine dosing may benefit p53 mutant AML, which is a large component in the sAML population. As a better understanding of the molecular aspects of de novo AML and sAML is gained, the mutations and mechanisms of sAML should be better targeted, leading to improved efficacy and safety.

DISCLOSURE

Advisory Board: Jazz Pharmaceuticals, Pfizer Inc.

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