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Challenges in the diagnosis and treatment of secondary acute myeloid leukemia

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ABSTRACT

Secondary AML (sAML), referring to AML arising after prior cytotoxic/radiation/immunosuppressive therapy (tAML) or an antecedent hematologic disorder, now primarily classified as AML with myelodysplasia-related changes (AML-MRC), accounts for 10%–30% of AML cases and is associated with a poor prognosis. sAML has historically been treated with intensive chemotherapy (eg, 7 + 3) or less aggressive regimens (eg, low-dose cytarabine or azacytidine for older/unfit patients); however, outcomes are typically poor, especially for older adults. Recently, CPX-351, a liposomal co-encapsulation of cytarabine and daunorubicin at a synergistic ratio, demonstrated improved front-line outcomes in older patients with high-risk/sAML. CPX-351 has been approved for adults with newly diagnosed tAML or AML-MRC and has an NCCN category 1 recommendation for induction therapy of patients aged > 60 years with high-risk/sAML. Other novel therapies may also benefit certain sAML subgroups. Greater clarity around the optimal diagnosis and treatment of sAML patients is needed to improve outcomes in this high-risk subpopulation.

1. Introduction

The term secondary acute myeloid leukemia (sAML) refers to AML arising either after a prior hematologic disorder, such as myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm (MPN), or after exposure to cytotoxic agents or radiation therapy. (Leone et al., 1999) In total, sAML accounts for 10% to 30% of all AML cases (Leone et al., 1999). Most cases (60%–85%) of sAML progress from antecedent MDS, while therapy-related (tAML) accounts for 15% to 40% of all sAML cases (Leone et al., 1999). The proportion of AML patients with sAML increases with age. Before age 40, tAML and AML with an antecedent hematologic disorder each constitute about 3% of all AML cases; after age 40, the prevalence of tAML and AML with an antecedent hematologic disorder increase to approximately 10% and 20% of all AML cases, respectively (Hulegardh et al., 2015). Across multiple studies, sAML has been associated with inferior outcomes, including lower remission rates and shortened overall survival (OS), compared with *de novo* AML. (Hulegardh et al., 2015; Granfeldt Ostgard et al., 2015; Szotkowski et al., 2010; Xu et al., 2014), Thus, a good understanding of sAML and its optimal treatment is important. This review discusses unmet needs for this challenging population.

2. Current diagnostic criteria and pathogenesis of sAML

2.1. tAML

tAML is an AML subtype that occurs in patients who were previously treated with chemotherapy, radiotherapy, or immunosuppressive therapy for an unrelated malignancy or immune disorder. (Heuser, 2016; Godley and Larson, 2008) Most cases of chemotherapy-induced tAML result from cytotoxic drugs that fall into 2 groups: (1) alkylating agents, including melphalan, cyclophosphamide, and nitrogen mustard, or (2) agents targeting topoisomerase, including etoposide, doxorubicin, daunorubicin, and mitoxantrone (Leone et al., 2007). Notably, the 2008 revision to the WHO classification acknowledged that many patients who develop tAML have received multiple types of prior therapy, and as such, no subclassification of patients with tAML based on type of prior therapy is necessary (Vardiman et al., 2009).

The pathogenesis of tAML may occur by direct induction of a fusion oncogene through chromosomal translocation, induction of genome instability, or selection of pre-existing treatment-resistant hematopoietic cell clones. (Heuser, 2016) Recent evidence has corroborated the model of tAML development that proposes clonal expansion under the selective pressure of chemotherapy. *De novo* AML and tAML exhibit

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a similar percentage of chemotherapy-related transversions and number of somatic nucleotide variants, suggesting prior chemotherapy may not inflict genome-wide DNA damage. (Wong et al., 2015) In addition, pre-leukemic clonal hematopoiesis is frequently detected in the peripheral blood and/or bone marrow of patients with therapy-related neoplasms at the time of their primary cancer diagnosis, before the initiation of chemotherapy or radiotherapy (Takahashi et al., 2017). Mutations in *TP53* (the most commonly mutated gene in tAML, but not *de novo* AML [33% vs 13% of patients, respectively]) have been detected at low frequencies in tAML patients prior to the development of tAML or therapy-related MDS (tMDS) and, in some patients, prior to any chemotherapy; *TP53* mutations were also present in peripheral blood cells of healthy chemotherapy-naïve elderly individuals. (Wong et al., 2015; Ok et al., 2015a) Taken together, these data indicate chemotherapy may not directly induce *TP53* mutations, but rather that hematopoietic stem/progenitor cells harboring age-related *TP53* mutations may preferentially expand after treatment with chemotherapy. (Wong et al., 2015)

2.2. AML with an antecedent hematologic disorder

The WHO classification of patients with AML with an antecedent hematologic disorder, most of whom fall under the category of AML with myelodysplasia-related changes (AML-MRC), has evolved over the past decade. The WHO introduced the classification of AML-MRC in 2008, expanding upon the prior classification of AML with multilineage dysplasia classification to also include patients with specific myelodysplasia-related cytogenetic abnormalities. The changes occurred after several studies showed that morphologic multilineage dysplasia had no independent prognostic significance after incorporating cytogenetic findings into the analysis. (Vardiman et al., 2009) In 2016, the WHO diagnostic criteria for AML-MRC (Table 1) was then modified such that multilineage dysplasia in > 50% of ≥2 cell lineages was no longer sufficient to categorize AML-MRC in the presence of *NPM1* or biallelic *CEBPA* mutations. This modification reflected the lack of prognostic significance of multilineage dysplasia in patients with *NPM1* or biallelic *CEBPA* mutations. (Arber et al., 2016) Thus, according to the most recent WHO classification (2016), the AML-MRC designation applies to AML patients who have ≥20% blasts in blood or bone marrow and who meet any of the following criteria: (1) a history of MDS or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), (2) an MDS-related cytogenetic abnormality, or (3) multilineage dysplasia in > 50% of ≥2 cell lineages in the absence of *NPM1* or biallelic *CEBPA* mutations. (Vardiman et al., 2009; Arber et al., 2016; Vardiman and Reichard, 2015) Meanwhile, an AML-MRC diagnosis excludes tAML and AML with any of the cytogenetic abnormalities that qualify for diagnosis of AML with recurrent genetic abnormalities, such as *NPM1* or biallelic *CEBPA* mutations. (Weinberg and Arber, 2010) As a result, a subset of patients with sAML with an antecedent hematologic disorder meet the criteria for AML with recurrent genetic abnormalities, rather than AML-MRC.

Whole genome sequencing was utilized to study the genetic changes that underlie progression from MDS to sAML. (Walter et al., 2012) It was found that nearly all bone marrow cells in patients with MDS or sAML are clonally derived. In every case, progression from MDS to sAML entailed the persistence of an antecedent founding clone containing hundreds of somatic mutations and the outgrowth of > 1 subclone harboring dozens to hundreds of new mutations. During this progression, acquired mutations often disrupt normal hematopoietic differentiation (eg, mutations in *RUNX1*, *GATA2*, and *CEBPA*) and/or activate signaling pathways that control proliferation (eg, mutations in *FLT3* or *RAS* family members). (Sperling et al., 2017)

Table 1
Classification and differential diagnosis of patients with sAML according to the 2016 WHO criteria.

Clinical assessment	Classification of patients with sAML		
	tAML	AML-MRC	AML with recurrent genetic abnormalities
Blast counts	≥20% blasts in peripheral blood or bone marrow		
Clinical history	Prior treatment with chemotherapy, radiotherapy, or immunosuppressive therapy for an unrelated malignancy or immune disorder	A history of MDS or MDS/MPN	A history of MDS or MDS/MPN
Morphological features	NA	Multilineage dysplasia (ie, dysgranulopoiesis, dyserythropoiesis, and/or dysmegakaryopoiesis) in > 50% of ≥2 cell lineages in the absence of genetic abnormalities defining the category of recurrent genetic abnormalities	NA
Cytogenetic abnormalities/ genetic mutations (assessed via FISH or RT-PCR)	NA	1 ≥3 unrelated abnormalities, not including the recurrent genetic abnormalities encountered in AML 2 Unbalanced abnormalities: 3 −7/del(7q) 4 del(5q)/t(5q) 5 i(17q)/t(17p) 6 −13/del(13q) 7 del(11q) 8 del(12p)/t(12p) 9 idic(X)(q13) 10 Balanced abnormalities: 11 t(11;16)(q23.3;p13.3) 12 t(3;21)(q26.2;q22.1) 13 t(1;3)(p36.3;q21.2) 14 t(2;11)(p21;q23.3) 15 t(5;12)(q32;p13.2) 16 t(5;7)(q32;q11.2) 17 t(5;17)(q32;p13.2) 18 t(5;10)(q32;q21.2) 19 t(3;5)(q25.3;q35.1)	1 t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* 2 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* 3 *PML-RARA* 4 t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* 5 t(6;9)(p23;q34.1); *DEK-NUP214* 6 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM* 7 t(1;22)(p13.3;q13.3); *RBM15-MKL1* 8 Mutated *NPM1* 9 Biallelic mutations of *CEBPA*

sAML, secondary acute myeloid leukemia; WHO, World Health Organization; tAML, therapy-related acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; MDS, myelodysplastic syndrome; MDS/MPN, myelodysplastic/myeloproliferative neoplasm; NA, not applicable; FISH, fluorescent in situ hybridization; RT-PCR, reverse transcription polymerase chain reaction.

The term MPN refers to clonal proliferation of mature myeloid elements, leading to an excess of platelets (essential thrombocytosis), red blood cells (polycythemia vera), or white blood cells (primary myelofibrosis). (Tefferi and Vardiman, 2008) In a series of 218 patients, leukemic transformation occurred in 2%, 4%, and 11% of patients with essential thrombocytosis, polycythemia vera, and primary myelofibrosis, respectively, over an 18-year period (Cervantes et al., 1991). Notably, some cases of AML also evolve from MDS/MPN overlap syndromes (eg, chronic myelomonocytic leukemia), in which myeloid neoplasms exhibit features of and harbor mutations associated with both MDS and MPN. To investigate the pathogenesis of post-MPN sAML, high-throughput sequence analysis compared the somatic mutational spectrum of post-MPN sAML and *de novo* AML. (Rampal et al., 2014) The spectrum of genomic alterations differed greatly between post-MPN sAML and *de novo* AML, suggesting a unique molecular pathogenesis of post-MPN sAML. Post-MPN sAML was frequently characterized by mutations in *CALR*, *JAK2*, *TP53*, *IDH2*, and *ASXL1*; in contrast, common mutations in *de novo* AML (eg, *NPM1*, *FLT3*, and *CEBPA* mutations) were rare in post-MPN sAML. Further preclinical assessment demonstrated that *JAK2* V617 F mutations in conjunction with *TP53* loss led to fully penetrant AML in murine models. Taken together, the results of this study lend insight into the molecular pathogenesis of post-MPN sAML. (Rampal et al., 2014)

2.3. Differential diagnosis of patients with sAML

With the recent changes to the WHO classification of AML, greater clarity is needed to properly diagnose patients with sAML to ensure they receive optimal treatment. Table 1 provides an overview of diagnostic criteria for the various AML subcategories that encompass patients with sAML, including tAML, AML-MRC, and those classified as having AML with recurrent genetic abnormalities. In the clinic, obtaining a thorough patient history can differentiate cases of tAML from other AML subtypes, based on prior treatment with chemotherapy, radiotherapy, or immunosuppressive therapy for an unrelated malignancy or immune disorder. Furthermore, fluorescent in situ hybridization and/or reverse transcription polymerase chain reaction testing should be used to distinguish patients with AML-MRC from those with AML with recurrent genetic abnormalities, based on their cytogenetic and/or mutational profiles. Therefore, timely reporting of results from cytogenetic testing and mutational analyses is important to facilitate a complete diagnosis. Collectively, these steps will ensure a proper diagnosis of patients with sAML and, based on that diagnosis, help guide the selection of optimal therapies. In the future, the role of mutational analyses in classifying AML patients may further expand, as studies continue to delineate more precise genomic profiles specific to *de novo* AML, tAML, and AML-MRC. (Lindsley et al., 2015) Since the diagnostic categorization of AML patients relies in part on clinical history, which is inherently inexact, further refinement of cytogenetic and mutational analyses may help to facilitate more accurate and specific diagnoses of AML patients.

3. Traditional standard of care and typical outcomes in patients with sAML

In patients deemed fit for intensive chemotherapy, initial treatment of sAML has traditionally involved induction with a combination chemotherapy regimen, such as continuous multiple-day infusion of cytarabine plus multiple-day infusions of an anthracycline. (Fey et al., 2013; National Comprehensive Cancer Network, 2019) In the United States and Europe, the 7 + 3 regimen, which consists of continuous cytarabine infusion for 7 days with 3 days of an anthracycline (ie, daunorubicin or idarubicin) is considered a standard of care for induction, National Comprehensive Cancer Network, 2019; De Kouchkovsky and Abdul-Hay, 2016; Dohner et al., 2017) although other regimens are also used. Depending on various risk factors, patients achieving complete remission (CR) with induction are subsequently treated with consolidation chemotherapy and/or allogeneic hematopoietic stem cell transplantation (HSCT). (De Kouchkovsky and Abdul-Hay, 2016) Compared with patients with *de novo* AML, patients with sAML tend to be older and have more significant comorbidities, a poorer Eastern Cooperative Oncology Group (ECOG) performance status, and, consequently, a higher risk of treatment-related mortality with intensive induction therapy. (Szotkowski et al., 2010; Schoch et al., 2004; Kayser et al., 2011) To mitigate this risk, some patients with sAML elect to receive less intensive therapy, such as hypomethylating agents (HMAs), which can induce remission and potentially prolong OS (Zeichner and Arellano, 2015).

Despite the use of intensive chemotherapy regimens, the prognosis of patients with sAML remains poor, especially for older patients. In analyses of several large population-based AML cohorts, sAML was associated with inferior outcomes, including lower remission rates and shortened OS, compared with *de novo* AML. (Hulegardh et al., 2015; Granfeldt Ostgard et al., 2015; Szotkowski et al., 2010; Xu et al., 2014) Both AML with an antecedent hematologic disorder and tAML have been identified as independent risk factors for poor OS (Hulegardh et al., 2015), although a patient's specific prognosis also depends on other factors, such as the presence of certain cytogenetic abnormalities. Induction treatment of tAML has typically been associated with a poor prognosis, with a median OS of only 6 months (Bhatia, 2013). With conventional chemotherapy, median disease-free survival (DFS) and OS were reported as 5 and 10 months, respectively, in patients with AML-MRC (patients with antecedent MDS or MDS/MPN comprised ˜20% of this patient population). (Xu et al., 2014) Furthermore, standard induction chemotherapy has not improved outcomes in post-MPN sAML patients, as OS was similarly short in patients who received induction chemotherapy, low-intensity chemotherapy, or supportive care (Mesa et al., 2005).

Due to the lack of sustained response to conventional induction chemotherapy, allogeneic HSCT is often recommended for patients with sAML who achieve CR, are in good general condition, and have a suitable donor. (Bhatia, 2013; Li et al., 2018) HSCT can be an effective treatment for patients who have responsive disease without poor-risk cytogenetics (Yakoub-Agha et al., 2000; Litzow et al., 2010). In a large, systemic analysis of the European Society for Blood and Bone Marrow Transplantation registry, OS and DFS at 2 years were 45% and 39%, respectively, in sAML patients who received HSCT (Sengsayadeth et al., 2018). In this study, active disease, poor-risk cytogenetics, older age, lower ECOG performance score, and other comorbid hematologic malignancies were all associated with inferior OS and DFS. In patients with post-MPN sAML, those receiving induction chemotherapy alone had a median OS of only 4 months, while those receiving induction chemotherapy followed by HSCT had a median OS between 6 and 9 months (Mesa et al., 2005; Kennedy et al., 2013).

4. Prognostic factors in sAML

Consistent with the general AML population, a number of factors have been shown to influence prognosis in patients with sAML, including age, fitness, cytogenetic profile, and genetic mutations.

4.1. Age

Compared with *de novo* AML, patients with sAML tend to be older, are more likely to have adverse cytogenetics, and are less commonly treated with curative intention. (Szotkowski et al., 2010; Schoch et al., 2004; Kayser et al., 2011) A number of studies have investigated the prognostic value of sAML in older and younger cohorts of patients, but with conflicting conclusions. In one study, the impact of sAML on OS was age-dependent, as sAML strongly impacted OS in younger AML patients, yet it lacked prognostic value among elderly patients (Hulegardh et al., 2015). In contrast, another population-based study

identified sAML as an unfavorable prognostic marker for OS in both patients under and over 60 years of age (Szotkowski et al., 2010). Further addressing the prognostic impact of sAML in both older and younger adult patients, a separate study assessed post-remission cumulative incidence of death (CID) and cumulative incidence of relapse (CIR) in patients with tAML from both age subgroups (Kayser et al., 2011). In intensively treated patients aged ≤60 years, CID, but not CIR, was significantly greater in patients with tAML versus *de novo* AML, likely reflecting the cumulative toxicity of primary and secondary cancer treatments. In contrast, in less intensively treated patients aged > 60 years, CIR, but not CID, was significantly greater in patients with tAML versus *de novo* AML, likely reflecting the lower dose of post-remission chemotherapy administered to older patients.

A number of studies have also investigated age as a prognostic factor in patients with sAML. In a cohort of patients with tAML (n = 93) or *de novo* AML (n = 1091), multivariate Cox regression analysis found age to be independently and significantly related to OS; however, univariate Cox regression analyses found no significant correlation between age and OS in the subgroup of patients with tAML. (Schoch et al., 2004) In a cohort of 302 patients with AML, including 115 cases of AML-MRC and 187 cases of AML not otherwise specified (AML-NOS), a multivariate analysis demonstrated that age ≥60 years was an independent negative prognostic factor for OS and DFS (Xu et al., 2014). However, in a study that focused exclusively on patients with AML-MRC (n = 125), a multivariate analysis found no significant correlation between age and either CR rate or OS (Devillier et al., 2015a).

4.2. Performance status

ECOG performance status > 2 is an unfavorable prognostic factor in AML, including patients with sAML. (Zeichner and Arellano, 2015) Patients with a poor performance status have a higher risk of dying during induction chemotherapy and often require treatment with less intensive therapy (eg, HMA therapy) (Zeichner and Arellano, 2015). Notably, CR rates and OS have been reported as significantly worse in patients with either tAML or AML-MRC compared with those with *de novo* AML, regardless of ECOG performance status. (Hulegardh et al., 2015)

4.3. Cytogenetics

In tAML, both favorable and unfavorable cytogenetics have been reported as strong prognostic factors for OS, independent of age and white blood cell count. (Schoch et al., 2004) Similarly, cytogenetics was found to be the strongest prognostic factor for OS in a cohort of patients with AML who underwent HSCT; in this cohort, patients with tAML/tMDS who had adverse cytogenetics had significantly shorter OS and DFS compared with those who had favorable cytogenetics (Armand et al., 2007). After accounting for cytogenetics, patients with tAML/tMDS had equivalent outcomes (including OS and DFS) to patients with *de novo* AML. (Armand et al., 2007) For example, patients with tAML who had cytogenetic abnormalities that predict a favorable risk, such as t(8;21) or t(8;16), have nearly identical treatment responses as *de novo* patients with the same cytogenetic abnormalities. (Quesnel et al., 1993; Grimwade et al., 2001) In contrast, another study identified tAML as an unfavorable prognostic factor for OS, independent of cytogenetics; in this study, the negative prognostic impact of tAML was most pronounced in patients with favorable cytogenetics (Schoch et al., 2004). Given these contradictory results, it remains unclear whether tAML portends a poor outcome independent of cytogenetics.

In a cohort of 302 patients with AML (115 cases of AML-MRC and 187 cases of AML-NOS), an unfavorable karyotype, MDS-related cytogenetics, and a history of MDS or MDS/MPN were all negative prognostic factors. (Xu et al., 2014) Another group assessed the prognostic value of the AML-MRC classification among AML patients with intermediate-risk cytogenetics to address the potentially confounding factor of cytogenetics (Devillier et al., 2015b). They compared patients with AML-MRC (22% of whom had a prior history of MDS) and patients with AML-NOS. Their results suggested the AML-MRC criteria do not carry prognostic value (concerning remission rates and OS) among patients with intermediate-risk cytogenetics; consequently, they propose comprehensive mutation screening to help further refine AML classification. Taken together, these results emphasize the paramount importance of a patient's cytogenetic profile, rather than disease phenotype, in predicting treatment response.

4.4. Genetic mutations

Due to their robust prognostic significance in AML, genetic mutations are routinely assessed in current clinical practice. (Dohner et al., 2017) Although a number of genetic mutations have been identified in AML, overlap exists between the AML subclassifications. However, research aimed at further refining the mutational characterization of different AML subtypes may help to delineate more precise genomic profiles and thereby improve diagnosis (Lindsley et al., 2015).

The most frequently mutated genes in a cohort of 42 patients with tAML were *TP53* (36%), *PTPN11* (12%), *IDH1* (10%), *IDH2* (10%), *NRAS* (10%), *FLT3* (7%), *DNMT3A* (7%), and *KRAS* (5%). (Ok et al., 2015a) Mutations and loss of heterozygosity of *TP53* are common (reported in 17%–37% of patients across studies) and associated with a poor prognosis in patients with tMDS or tAML. (Christiansen et al., 2001; Ok et al., 2015b) Multivariate analysis of 108 patients with tMDS or tAML identified *TP53* mutations as an independent negative prognostic factor for OS. (Ok et al., 2015b) Amplification of the *MLL* gene was also commonly observed in patients with tMDS or tAML (17%), and these patients showed shorter OS compared with patients without these mutations. (Andersen et al., 2001)

The most frequently reported mutations in patients with AML-MRC (according to the 2008 WHO criteria) were *ASXL1* (35% of patients), *IDH/IDH2* (25%), *RUNX1* (17%), *TET2* (15%), *DNMT3A* (8%), and *FLT3* (2%) mutations. (Devillier et al., 2012) Thus, AML-MRC is characterized by a high frequency of *ASXL1* mutations and a low frequency of mutations in *FLT3* and *DNMT3A*. In a cohort of patients with AML-MRC (47% of whom had previously diagnosed MDS), *ASXL1* and *TP53* mutations identified a subset of patients with a particularly poor prognosis, characterized by shorter OS compared with patients without these mutations. (Devillier et al., 2015a)

5. Novel therapeutic approaches

Unfortunately, patients with sAML are often excluded from clinical trials, which limits the data available in this population. (Hulegardh et al., 2015) In the past couple years, many novel therapies have been approved for the treatment of AML, including CPX-351, venetoclax, gemtuzumab ozogamicin (GO), glasdegib, and multiple agents targeting IDH or FLT3. Some of these agents have been evaluated in patients with sAML, as discussed herein. The potential benefit of emerging therapies in earlier stages of clinical development for AML, such as chimeric antigen receptor T cells or agents targeting the TP53 pathway (eg, idasanutlin), should similarly be evaluated in patients with sAML in future clinical trials.

5.1. CPX-351 chemotherapy

CPX-351 (Vyxeos®, Jazz Pharmaceuticals) is a liposomal co-encapsulation of cytarabine and daunorubicin that delivers a synergistic drug ratio preferentially to leukemia cells. (Kim et al., 2011; Lim et al., 2010) Although the active agents in CPX-351 are the same as those in the conventional 7 + 3 regimen, the CPX-351 liposomes provide benefits with regard to drug pharmacokinetics, maintenance of the synergistic drug ratio, and delivery and accumulation of drug in the bone marrow. Unlike many other liposomal drug formulations that focus

primarily on improving the drug safety profile, CPX-351 was designed to improve the anti-leukemia activity.

A subgroup analysis of a phase 2 study in older patients with newly diagnosed sAML found a significant improvement in median OS with CPX-351 (12.1 months) versus conventional 7 + 3 cytarabine and daunorubicin regimen (6.1 months; hazard ratio 0.46; $P = 0.01$). (Lancet et al., 2014) CPX-351 treatment was also associated with significantly improved median EFS (4.5 vs 1.3 months; hazard ratio = 0.59; $P = 0.08$) and a higher remission rate (CR or CR with incomplete recovery of platelets or neutrophils [CRi]; 58% [n = 19/33] vs 32% [n = 6/19]; $P = 0.06$) versus 7+3 in sAML patients.

In a subsequent pivotal randomized, phase 3 trial (N = 309), CPX-351 significantly improved median OS (9.56 months) compared with 7 + 3 (5.95 months; hazard ratio = 0.69; one-sided $P = 0.003$) in older adults (aged 60–75 years) with newly diagnosed high-risk/sAML who were considered fit for intensive chemotherapy. (Lancet et al., 2018) CPX-351 was also associated with significantly higher rates of CR + CRi (48%) versus 7 + 3 (33%), including 37% and 26% of patients with CR, respectively. The higher remission rate also permitted a greater proportion of patients receiving CPX-351 to proceed to HSCT (34% vs 25%), and median OS landmarked from the time of HSCT was longer with CPX-351 versus 7 + 3 (not reached vs 10.25 months). The safety profile of CPX-351 was generally similar to that of 7 + 3 in this study, and was consistent with the known profile of 7 + 3, although the median time to neutrophil and platelet recovery in patients achieving CR or CRi was longer with CPX-351. Importantly, this trial established CPX-351 as the first agent to achieve superior outcomes compared with standard-of-care chemotherapy (7 + 3 regimen) in this poor prognosis subset of AML patients. Consequently, CPX-351 was approved by the US Food and Drug Administration (FDA) in 2017 and by the European Medicines Agency (EMA) in 2018 for the treatment of adults with newly diagnosed tAML or AML-MRC (Talati and Lancet, 2018), and is currently the only newer therapy that is approved for these AML subpopulations. CPX-351 is also the only agent with a category 1 recommendation by the National Comprehensive Cancer Network for induction therapy for patients aged ≥60 years who are candidates for intensive remission induction therapy and have tAML, AML with antecedent MDS or chronic myelomonocytic leukemia, or AML with cytogenetic changes consistent with MDS (AML-MRC); CPX-351 additionally has a category 2B recommendation for patients aged < 60 years with these AML subtypes. (National Comprehensive Cancer Network, 2019). The European LeukemiaNet panel also noted in their 2017 recommendations that CPX-351 induction was expected to improve the treatment of older patients with high-risk features (Dohner et al., 2017), such as those with sAML, although CPX-351 was not yet approved when the recommendations were published. In addition, these promising results could open the door for combination regimens with targeted therapies, using CPX-351 as a backbone therapy in place of conventional 7 + 3 chemotherapy, in patients with sAML. For example, the combination of CPX-351 with an FLT3 inhibitor may improve outcomes for patients with *FLT3* mutations, since CPX-351 demonstrated an improved remission rate versus 7 + 3 in this subset of patients in the phase 3 trial (CR + CRi: 68% vs 24% with 7 + 3).

5.2. Bcl-2 inhibitors

Unlike normal hematopoietic stem cells that mostly depend on Mcl-1 for survival, AML cells depend on anti-apoptotic Bcl-2. (Mihalyova et al., 2018) Thus, as a small-molecule inhibitor of Bcl-2, venetoclax (Venclyxto/Venclexta®, AbbVie) selectively targets AML cells (Mihalyova et al., 2018). Combining venetoclax with lower-intensity anti-leukemia agents, such as low-dose cytarabine (LDAC) or HMAs, has demonstrated promising activity in older patients with treatment-naïve AML who are unfit for intensive chemotherapy. (Wei et al., 2018; DiNardo et al., 2019), In a phase 1/2 study of venetoclax plus LDAC in older patients with untreated AML, a CR + CRi rate of 54% (n = 44/82) has been observed; of the patients who achieved CR + CRi, 32% (n = 14/44) were negative for minimal residual disease (assessment $< 10^{-3}$). (Wei et al., 2018) In this trial, 49% of patients had secondary AML (60% of whom had prior HMA exposure); the CR + CRi rate in this patient subgroup was 35%. A phase 1b study of venetoclax plus HMA therapy (decitabine or azacitadine) in older patients with untreated AML demonstrated a CR + CRi rate of 67% (n = 97/145) in the overall study population. Among patients who achieved CR + CRi, 29% (n = 28/97) were negative for minimal residual disease. The CR + CRi rate was 67% (n = 24/36) in the subset of patients with sAML; notably, patients who had previously received treatment with an HMA and/or chemotherapy for an antecedent hematologic disorder were excluded from the trial (DiNardo et al., 2019). Based on these clinical data, the combination of venetoclax with LDAC, azacitidine, or decitabine was granted accelerated approval by the US FDA in 2018 for the treatment of newly diagnosed AML in adults who are aged ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy. (VENCLEXTA®, 2018) However, since this approval was based on early-phase studies, continued FDA approval for this indication is contingent upon verification of clinical benefit in confirmatory trials.

Adults with relapsed/refractory AML treated with the combination of venetoclax and HMAs were analyzed retrospectively. (Aldoss et al., 2018) The overall response rate was 64%, with CR, CRi, and morphologic leukemia-free state achieved by 30%, 21%, and 12% of patients, respectively. The CR + CRi rate was numerically, but not significantly, higher for patients with *de novo* AML (61%) or tAML (60%) compared with those with an antecedent hematologic disorder (0%; $P = 0.067$).

5.3. Anti-CD33 therapy

CD33 is expressed by blasts in most patients with AML, but not by normal hematopoietic stem cells. (Appelbaum and Bernstein, 2017) Taking advantage of the selective expression of CD33 by blasts, GO *(Mylotarg™, Pfizer)* was developed as a conjugate of an anti-CD33 antibody and the toxin calicheamicin. (Appelbaum and Bernstein, 2017; Jen et al., 2018) GO was approved by the FDA in 2017 and the EMA in 2018 in combination with standard cytarabine and daunorubicin for the treatment of adult patients with newly diagnosed, CD33-positive AML; GO was also approved by the FDA as monotherapy for the treatment of patients ≥2 years of age with relapsed/refractory, CD33-positive AML.

A few recent clinical trials have evaluated the potential of adding GO to traditional chemotherapy regimens for the treatment of patients with sAML. In a phase 2 study that assessed GO in combination with chemotherapy (idarubicin plus cytarabine) in untreated patients with high-risk MDS or AML evolved from MDS, the CR + CRi rate was 43%. (de Witte et al., 2015) According to the statistical design of the study, this regimen did not show sufficient activity to warrant further exploration in adults with high-risk MDS or sAML, as this CR + CRi rate was lower than those observed in response to various intensive chemotherapy regimens. A phase 3 trial also did not find improved survival or remission rates with the addition of GO to various chemotherapy induction/consolidation regimens (including cytarabine/daunorubicin, cytarabine/daunorubicin/etoposide, and fludarabine/cytarabine/granulocyte colony-stimulating factor/idarubicin) among the subgroups of patients with sAML or high-risk cytogenetics. (Burnett et al., 2011)

5.4. Hedgehog pathway inhibitors

The hedgehog pathway plays an important role in the maintenance and expansion of leukemic stem cells, as well as the acquisition of a drug-resistant phenotype in AML. (Aberger et al., 2017; Campbell and Copland, 2015) Glasdegib (Daurismo™, Pfizer) blocks hedgehog signaling by inhibiting smoothened, a transmembrane receptor with an integral role in the canonical hedgehog pathway. (DAURISMO™, 2018) In a randomized, phase 2 study, the combination of glasdegib plus

LDAC prolonged OS and achieved a higher CR rate compared with LDAC alone in patients with newly diagnosed AML or high-risk MDS who were unsuitable for intensive chemotherapy (Cortes et al., 2019). Consequently, the combination of glasdegib plus LDAC was approved by the FDA in 2018 for adults with newly diagnosed AML who are aged ≥75 years or have comorbidities that preclude the use of intensive induction chemotherapy (DAURISMO™, 2018). Patients with tAML or AML with an antecedent hematological disorder were included in the phase 2 study; however, a subanalysis of outcomes in these patients has not yet been reported.

5.5. IDH inhibitors

Leukemic *IDH1* and *IDH2* mutations disrupt hematopoietic differentiation, thereby enriching for stem cell populations and promoting leukemogenesis. (Figueroa et al., 2010) Mutations in *IDH1* occur in approximately 6%–10% of patients with AML and *IDH2* mutations occur in approximately 9%–13% of patients. (DiNardo et al., 2018) Among patients with tAML, both *IDH1* and *IDH2* mutations have been reported at a frequency of 10% (Ok et al., 2015a); among patients with AML-MRC, *IDH1* and *IDH2* mutations have been reported at a frequency of 4% and 21%, respectively. (Devillier et al., 2012)

Ivosidenib (Tibsovo®, Agios) and enasidenib (Idhifa®, Celgene) promote myeloid differentiation and reduce blast counts by inhibiting mutant IDH1 and mutant IDH2, respectively. (IDHIFA®, 2017; TIBSOVO®, 2018) Ivosidenib was approved by the FDA in 2018 for adults with relapsed/refractory *IDH1*-mutated AML, and enasidenib was approved by the FDA in 2017 for adults with relapsed/refractory *IDH2*-mutated AML (IDHIFA®, 2017; TIBSOVO®, 2018). The approval of ivosidenib was based on promising results of a phase 1 trial, in which a CR + CRi rate of 30% was observed in adults with relapsed/refractory *IDH1*-mutated AML receiving ivosidenib monotherapy. (DiNardo et al., 2018) Patients with tAML, AML with antecedent MDS, and AML with antecedent MPN represented 9%, 21%, and 5% of the study population, respectively; however, outcomes were not reported for these AML subtypes. Meanwhile, the approval of enasidenib was based on a first-in-human phase 1/2 trial of enasidenib monotherapy, in which a CR + CRi rate of 26% and median OS of 9.3 months were reported in adults with relapsed/refractory *IDH2*-mutated AML. (Stein et al., 2017) In this study, patients with AML-MRC and tAML constituted 27% and 2% of the patient cohort, respectively; however, outcomes in these patient subgroups were not analyzed.

5.6. FLT3 inhibitors

Many patients with AML have an activating mutation in the transmembrane receptor tyrosine kinase *FLT3*, which predicts a poor prognosis. (Stone et al., 2018) Notably, the *FLT3*-ITD mutation occurs less frequently in patients with sAML (encompassing both AML with an antecedent hematologic disorder and tAML) than in patients with *de novo* AML (9% vs 26%, respectively). (Frohling et al., 2002) Similarly, the incidence of the *FLT3*-ITD mutation is less common in AML with antecedent MDS (12%–15%) than in the general population of adults with newly diagnosed AML (20%–25%). (Thiede et al., 2002; Levis, 2013)

Midostaurin (Rydapt®, Novartis), a small-molecule inhibitor of *FLT3*, was approved by the FDA and EMA in 2017 in combination with cytarabine and daunorubicin chemotherapy (specified as standard cytarabine/daunorubicin regimen in the United States) for the treatment of adult patients with newly diagnosed *FLT3*-mutated AML (Stone et al., 2018); in Europe, midostaurin is also approved for continued single-agent use in this population once the chemotherapy regimen is completed in patients who had responded to treatment. In a pivotal, randomized phase 3 trial, midostaurin plus conventional chemotherapy (induction therapy with cytarabine/daunorubicin, followed by consolidation therapy with high-dose cytarabine) prolonged OS and EFS compared with chemotherapy alone in patients aged ≤60 years with newly diagnosed AML with an *FLT3* mutation. (Stone et al., 2017) However, patients with tAML were excluded from this trial, and a subanalysis of outcomes in the small cohort of patients with sAML was not performed.

Several other FLT3 kinase inhibitors were recently granted approval or breakthrough therapy designation by the FDA for the treatment of patients with relapsed/refractory AML. Gilteritinib (Xospata®, Astellas Pharma) was approved by the FDA in 2018 for adults with relapsed/refractory *FLT3*-mutated AML, based on phase 3 results showing a CR + CRi rate of 21% in this patient population. (XOSPATA®, 2018) In addition, quizartinib (Daiichi Sankyo) was granted breakthrough therapy designation by the FDA in 2018 for adults with relapsed/refractory *FLT3*-ITD–mutated AML. (Daiichi-Sankyo, 2018) This designation was based on the results of a randomized, phase 3 trial demonstrating that single-agent quizartinib prolonged OS compared with salvage chemotherapy in patients with relapsed/refractory *FLT3*-ITD–mutated AML. (Cortes, et al., 2018) Patients with tAML were excluded from the aforementioned phase 3 trials for gilteritinib and quizartinib. Although patients with AML with antecedent MDS were included in both trials, data in this patient subset have not yet been reported for either trial.

6. Conclusion

The classification of patients with sAML continues to evolve, and sAML currently encompasses several subpopulations of patients, including those with tAML and some subpopulations classified as having AML-MRC. A good understanding of the sAML subtypes and their current diagnosis, based on the clinical history of the patient, morphological features, and molecular profile, is needed to guide treatment decisions. Patients with sAML historically have a poor prognosis and do not respond well to conventional intensive chemotherapy induction. Although patients with sAML are often excluded from clinical trials, certain novel agents have been evaluated in this patient subset. In a phase 3 trial, CPX-351 significantly prolonged OS and improved remission rates versus conventional 7 + 3 chemotherapy in patients with high-risk/sAML, leading to its approval by the FDA and EMA for adults with newly diagnosed tAML or AML-MRC. Furthermore, in phase 1/2 trials, venetoclax in combination with LDAC or HMAs demonstrated promising activity in the subset of patients with sAML who were considered unfit for intensive chemotherapy. In contrast, the addition of GO to standard chemotherapy regimens did not improve outcomes in patients with sAML. Glasdegib may benefit certain patients with sAML who are unsuitable for intensive chemotherapy, and IDH1/IDH2 inhibitors may benefit certain patients with relapsed/refractory sAML; however, evaluation of the efficacy of these agents in the sAML subpopulation is needed. Similarly, FLT3 inhibitors have not yet been evaluated specifically in patients with sAML, although the low incidence of *FLT3*-ITD mutations in sAML may limit their use in this patient population. Overall, greater clarity regarding the optimal treatment of patients with sAML is needed to improve outcomes in this high-risk subset of AML patients.

Conflict of interest

GO has received institutional research funding from Novartis, Janssen, Celgene, Immunogen, and BD; has been a paid consultant for Janssen, Sunesis, Celgene, and Roche; and has served on an advisory board for Novartis, Pfizer, Bristol-Myers Squibb, Janssen, Sunesis, Celgene, Amgen, Seattle Genetics, Roche, and Jazz. PM has received institutional research funding from Celgene, Daiichi Sankyo, Janssen, Karyopharm, Novartis, Pfizer, and Teva; has been a paid consultant for Celgene and Daiichi Sankyo; has served on an advisory board for AbbVie, Celgene, Daiichi Sankyo, Incyte, Janssen, Karyopharm, Novartis, Pfizer, Teva, and Jazz; and has participated in a speakers

bureau for Celgene, Daiichi Sankyo, Incyte, Janssen, Novartis, Pfizer, and Teva.

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