Secondary AML

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4.1 Introduction

Secondary acute myeloid leukemia (sAML) comprises all AML cases diagnosed after receiving cytotoxic agents, radiation therapy, immunosuppressive treatments, and those arising from prior hematologic disorders, such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) (Hulegårdh et al. 2015; Østgård et al. 2010; Godley and Larson 2008; Larson 2007). According to the 2016 World Health Organization (WHO) classification, the majority of sAML are included in two different entities, therapy-related myeloid neoplasms (t-MN) and AML with myelodysplasia-related changes (AML-MRC). However, AML-MRC not only contains sAML, but also de novo AML with certain criteria (see below) (Arber et al. 2016; Döhner et al. 2017). Although it is generally believed that a higher risk to develop a t-MN exists after a primary neoplasia, there is no consensus on whether it is due to an individual predisposition for developing tumors or a consequence of prior exposure to leukemogenic agents. The term AML with antecedent hematological disorders (AHD-AML) can be used for AML derived from MDS or MPN, but also for those cases in which a prior diagnosis of MDS or MPN was suspected on the basis of documented blood count abnormalities. The term AHD-AML has been abandoned by the WHO, and has been replaced by MRC-AML, which is more inclusive and accurate. As sAML patients achieve lower complete remission (CR) rates and shorter overall survival (OS) compared with de novo AML, the diagnosis of sAML has been considered an independent prognostic factor per se (Larson 2007; Stölzel et al. 2011; Pulsoni and Pagano 2005; Rizzieri et al. 2009). However, its independent prognostic value has been questioned because sAML is associated with other well-established adverse prognostic features such as older age, worse performance status (PS), and unfavorable cytogenetic or molecular profile (Østgård et al. 2010; Stölzel et al. 2011; Pulsoni and Pagano 2005; Rizzieri et al. 2009).

Secondary acute promyelocytic leukemia (sAPL) cases are almost exclusively diagnosed after a primary neoplasia treated with chemotherapy, radiotherapy, or immunosuppressive agents for a previous non-malignant disease, and the term therapy-related APL (t-APL) is recommended (Lo-Coco et al. 2013). In contrast to sAML, only anecdotal cases of sAPL evolving from MDS or MPN have been reported. The available evidence shows a relationship between developing t-APL and prior exposure to alkylating agents and topoisomer-

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ase II inhibitors (Beaumont et al. 2003; Mays et al. 2010; Mistry et al. 2005; Cowell and Austin 2012). Unlike sAML, main characteristics and clinical outcomes of t-APL seem similar to de novo APL, and prognosis of t-APL patients is significantly better than in patients with other t-MN (Lo-Coco et al. 2013; Pulsoni et al. 2002).

4.2 Epidemiology

The reported incidence of sAML ranges between 20 and 30% of all AML cases (Juliusson et al. 2009; Bertoli et al. 2017; Medeiros et al. 2015; Hulegårdh et al. 2015; Østgård et al. 2010, 2015; Gangatharan et al. 2013; Szotkowski et al. 2010). Nevertheless, the real frequency could be higher as sAML patients are usually excluded from clinical trials and protocols. Furthermore, it is difficult to calculate how many patients diagnosed with de novo AML had previously an undiagnosed MDS or MPN (Sengsayadeth et al. 2018). It is estimated that in two-thirds of patients, the sAML was preceded by MDS or MPN, whereas one-third of them are considered t-MN (86% related to cytotoxic agents or radiation therapy and 13% after immunosuppressive treatments) (Hulegårdh et al. 2015; Østgård et al. 2010). In patients younger than 40 years, t-AML occurs in about 5% of cases, and its prevalence increases up to 10% in patients above 40 years. Likewise, AHD-AML is uncommon before the age of 40 years, increasing up to 30% between 70 and 79 years (Hulegårdh et al. 2015). Table 4.1 shows the main studies reporting the frequency of sAML.

Regarding secondary APL, few studies have reported the frequency of t-APL, ranging from 15 to 21% of all APL cases (Braun et al. 2015; Beaumont et al. 2003; Elliott et al. 2012). Although overall t-APL incidence appears to be constant throughout the time, some authors suggest that evolving treatment strategies for breast cancer (with less frequent use of alkylating agents, topoisomerase II inhibitors, and anthracyclines) could have decreased its occurrence in this setting (Braun et al. 2015).

Table 4.1 Frequency of sAML

Author (Year) [Reference]	Age, years	sAML, %	AHD-AML, %	t-AML, %
Hulegårdh et al. (2015)	≥17	26.4	18.7 MDS-AML: 12.1 MPN-AML: 5.6	7.7
Østgård et al. (2010)	≥15	25	19 MDS-AML: 12 MPN-AML: 7	6 (24% of sAML)
Juliusson et al. (2009)	≥16	28	24	4
	70–74	38	32	6
Bertoli et al. (2017)	≥15	18	–	–
Medeiros et al. (2015)	>65	–	17.3	–
Østgård et al. (2015)	≥15	26.4	19.8	6.6 CHT:50.7 RT: 22.6 Both: 26.7
Gangatharan et al. (2013)	≥16	26	–	–
	>60	53	MDS-AML: 34 MPN-AML: 10	–
Nagel et al. (2017)	≥18	18	MDS-AML: 13.6	4.3
Wheatley et al. (2009)	≥60	22	–	–
Szotkowski et al. (2010)	≥18	25	MDS-AML: 15	10

sAML secondary acute myeloid leukemia, *AHD-AML* AML with an antecedent hematological disease, *t-AML* therapy-related AML, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *CHT* intensive chemotherapy, *RT* radiotherapy

4.3 Etiology and Pathogenesis

Prior exposure to cytotoxic drugs, radiation therapy, or immunosuppressive agents for treating neoplastic or non-neoplastic diseases are considered etiopathogenetic factors for the development

of t-AML. Several cytostatic drugs, such as alkylating agents or topoisomerase II inhibitors, have clearly been related to the development of sAML, and thus were defining pathological entities according to 2001 WHO classification (Mistry et al. 2005; Kayser et al. 2017; Schoch et al. 2004; Felix 1998). However, since the WHO 2008 version, these subgroups were no more independent entities (Vardiman 2008), and the t-AML definition included other types of therapy, as no practical advantages were expected from further subcategorizations. Although t-AML seems to increase with age (median age at diagnosis is around 69 years) (Østgård et al. 2010), it can be found in younger patients, too. It has been proposed that some younger patients may have inheritable predisposition to the development of t-AML (Godley and Larson 2008).

The pathogenesis of t-AML 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). The latter mechanism can explain the high frequency of *TP53* mutations in patients with t-AML. Longitudinal assessments performed in some t-AML patients showed that these mutations were detected at low-variant allele frequency before AML diagnosis and even before exposure to any cytotoxic therapy. Thus, it has been suggested that chemotherapy or radiotherapy may not directly induce *TP53* mutations but more probably select *TP53* mutated clones of hematopoietic progenitor cells, which may expand after treatment for primary neoplasia. Moreover, de novo AML and t-AML show a similar percentage of therapy-related transversions and number of somatic nucleotide variants, suggesting that prior treatment may not inflict genome-wide DNA damage (Wong et al. 2015; Takahashi et al. 2017; Ok et al. 2015a).

The genetic evolution from MDS to sAML is not well known. Studies based on whole genome sequencing have shown that bone marrow cells from patients diagnosed with MDS progressing to sAML are clonally derived throughout a dynamic process based on numerous cycles of mutation acquisition and clonal selection (Walter et al. 2012). During this progression, acquired mutations often interfere with normal hematopoietic differentiation (e.g., mutations in *RUNX1*, *GATA2*, and *CEBPA*) and/or activate signaling pathways that upregulate proliferation (e.g., mutations in *FLT3* or *RAS* family members) (Sperling et al. 2017).

Although the mechanisms and pathways that contribute to transformation from MPN to AML have not been well established, two distinct routes for leukemic transformation have been described: (1) *JAK2/MPL*-positive MPN progress to *JAK2/MPL*-positive AML—this pathway is associated with the acquisition of additional genetic alterations, and (2) *JAK2/MPL*-positive MPN progress to *JAK2/MPL*-negative AML, which are clonally related on account of a pre-*JAK2/MPL*-mutant clone (Zhang et al. 2012; Abdel-Wahab et al. 2010; Harutyunyan et al. 2011; Green and Beer 2010; Theocharides et al. 2007; Campbell et al. 2006). Some studies have shown that post-MPN-AML has a somatic mutational spectrum different from that observed in de novo AML (e.g., *JAK2*V617F mutations are rare in de novo AML, and AML patients with *JAK2*V617F mutations normally have a history of previous MPN; moreover common mutations in de novo AML, such as *NPM1* and *FLT3,* are usually absent in MPN-AML) (Fröhling et al. 2006a). In addition, MPN-AML is frequently characterized by mutations in *TP53*, *IDH2*, and *ASXL1*, and the acquisition of these somatic mutations may contribute to the progression from MPN to AML (e.g., loss of *TP53* in combination with expression of *JAK2V617F* results in the development of post-MPN-AML) (Rampal et al. 2014).

The latency period between diagnosis of the primary disease or previous cytostatic therapy and sAML can range from few months to several years. While the median latency was 1.1 years in MDS-AML (Hulegårdh et al. 2015), leukemic transformation occurs over a 10-year period in essential thrombocythemia (7.6 years), polycythemia vera (7.3 years), and primary myelofibrosis (Cervantes et al. 1991). Median latency time in t-AML can vary between 4.0 and 6.2 years, being shorter after malignancies (5.8 years) and

longer after non-malignant disorders (14.3 years) (Hulegårdh et al. 2015; Kayser et al. 2011). The latency period could depend on the cumulative dose, dose intensity, and type of preceding chemotherapy and/or radiation therapy (Godley and Larson 2008; Borthakur and Estey 2007). For instance, after receiving alkylating agents and/or radiation, patients can develop a t-AML in 5–10 years. However, patients who receive agents targeting topoisomerase II have often shorter latency period, approximately 1–5 years. In any case, such discrimination according to type of preceding therapy is not realistic, as patients often receive various types of agents. However, controversial data arise from some studies, which showed similar latency periods in patients with solid cancer who had not been exposed to previous therapy compared with those exposed to chemotherapy (Østgård et al. 2015). These findings suggest that, beyond clonal hematopoiesis selection or direct damage by leukemogenic agents, there might be a potential role of immune escape mechanisms in the pathogenesis of sAML in patients with a primary malignancy or autoimmune disease.

Regarding APL patients, those diagnosed with t-APL are older than those with de novo APL (mean age, 60.2 vs 48.7 years, respectively) (Braun et al. 2015). There is more prevalence of female gender, which may be related to the higher incidence of breast cancer and autoimmune diseases among primary disorders in female patients (Lo-Coco et al. 2013; Pulsoni et al. 2002; Kayser et al. 2017). The knowledge of the molecular pathogenesis of t-APL gained insights after identification of the role of DNA topoisomerase II (TOP2), a dimeric enzyme that plays an essential role in replication, transcription, chromosome condensation, and segregation. TOP2 facilitates one double-stranded DNA segment to pass through another, thus altering DNA topology. Before the re-ligation step, each monomer of TOP2 remains linked to DNA, forming double-strand breaks (DSB). Topoisomerase II inhibitors interfere in this re-ligation step, resulting in accumulation of DSB, which are cytotoxic and lead to apoptosis thought activation of the DNA damage response. Thus, chemotherapy-induced lesions are poorly repaired and generate a wide variety of genetic alterations like novel fusion genes, including t(15,17)(*PML-RARA*) (Mistry et al. 2005; Cowell and Austin 2012). Uneven distribution of DNA breakpoints at both *PML* and *RARA* loci suggest the existence of specific pathogenetic mechanisms in t-APL as compared with de novo APL (Hasan et al. 2010).

Latency between primary disorder and t-APL diagnosis ranges from few months to several years, with a median interval lower than 3.5 years (Kayser et al. 2017). Treatment with topoisomerase II-targeted drugs has commonly been related to shorter latency period, but recent studies suggested that only younger age at diagnosis of primary disorder was correlated with a shorter latency time (Beaumont et al. 2003; Kayser et al. 2011, 2017).

4.4 Clinical Features

Clinical presentation of sAML is variable and, similar to de novo AML, depending on three main factors: (1) bone marrow insufficiency, (2) presence of extramedullary disease, and (3) number of white blood cell (WBC) counts and presence of thrombogenic factors.

- Clinical features related to medullar insufficiency:
  - Anemia: weakness, fatigue, tachycardia, dyspnea, headache, etc.
  - Neutropenia: fever and infections
  - Thrombocytopenia: hemorrhage symptoms (coagulopathy, gingival bleeding, epistaxis, menorrhagia, etc.)
- Clinical features related to extramedullary disease:
  - Central nervous system (neurological disorders)
  - Hepatomegaly, splenomegaly, and lymphatic nodes
  - Skin (leukemia cutis)
  - Gingival hyperplasia
  - Granulocytic sarcoma

- Clinical features related to number of WBC and release of intracellular substances:
  - Leukostasis (frequently related to hyperleukocytosis): lungs (respiratory failure, infiltrates), central nervous system (neurological disorders without blast cells in cerebrospinal fluid)
  - Thrombogenic substances delivery (coagulopathy, disseminated vascular coagulopathy with fibrinogen decreased, and thrombosis)
  - Tumor lysis syndrome: hyperuricemia, creatinine increase, hypocalcemia, hyperkalemia, hyperphosphatemia

In relation with the aforementioned characteristics, some patients can present at diagnosis some specific features according to the type of sAML. MPNs are hematopoietic disorders characterized by clonal proliferation of mature myeloid elements that manifest clinically as an excess of red blood cells, platelets, or WBC (Campbell et al. 2006). In these instances, sAML may present clinical symptoms related to the previous MPN, such as hepatomegaly and splenomegaly, or other manifestations related to the increased number of peripheral blood cells. AML from MDS is usually less proliferative and t-AML patients can show signs and symptoms of hematopoietic insufficiency due to prior antineoplastic therapies, in addition to damage in different organs because of therapy-related sequalae (Appelbaum et al. 2006). Moreover, concomitant activity or relapse of previous tumors can complicate the clinical course of t-AML.

Characteristics of t-APL seem to be similar to de novo APL, with no differences reported for baseline hemoglobin, WBC, or platelets counts (Lo-Coco et al. 2013; Beaumont et al. 2003; Yin et al. 2005). However, like non-APL sAML, t-APL patients are older than de novo APL and have worse PS at diagnosis, which may determine the treatment choice and the outcomes (Lo-Coco et al. 2013; Pulsoni et al. 2002).

4.5 Diagnosis

Diagnosis of AML is based on morphological findings, so the detection of ≥20% blast cells in peripheral blood or bone marrow is a requisite, except for t(8;21), t(16:16)/inv(16), or t(15;17). Although dysplasia is frequent in sAML, its presence is not a diagnostic criteria (Arber et al. 2016; Döhner et al. 2017).

sAML diagnosis requires a documented clinical history of previous diagnosis of MDS, MPN, or MDS/MPN (AHD-AML); or prior treatment with chemotherapy, radiotherapy, or immunosuppressive therapy for an unrelated malignancy or immune disorder (t-AML).

Immunophenotypic characterization by multiparameter flow cytometry (MFC) can be helpful to support the diagnosis of sAML, distinguishing myeloid lineage from ambiguous, mixed, or lymphoid leukemias, which might be classified as different entities. Another utility of MFC is to detect the minimal residual disease (MRD) after initial therapy, allowing to establish relapse risk in order to adapt the intensity of post-remission strategies.

Cytogenetics and molecular tests remain mandatory in the assessment of AML, in order to complete diagnosis and to identify those sAML patients with favorable recurrent genetic abnormalities (RGAs) who may benefit from intensive approaches not including allogeneic stem cell transplant. In addition to conventional karyotyping, fluorescent in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) are useful tools to classify sAML patients. According to the 2017 panel of European Leukemia Net experts, genetic risk can be stratified in favorable, intermediate, and adverse, in both de novo AML and sAML.

The relevance of chromosomal alterations and gene variants for diagnosis, risk stratification, and choice of targeted therapies (i.e., FLT3 and IDH1/2 inhibitors) has remarkably increased the complexity of routine molecular diagnostic strategies. Next-generation sequencing (NGS) has been established as a new molecular diagnostic tool rapidly adopted by clinical laboratories, being

able to simultaneously assess different genetic alterations such as rearrangements, single nucleotide variants, insertions-deletions, and copy number variations in a wide variety of genes. NGS gene panels have been preferentially adopted rather than whole genome or exome sequencing due to an easier interpretation of results, lower cost, and less time. As compared to NGS, conventional single-gene approaches by PCR are laborious and less efficient to detect minor clones, but they are still needed as rapid-screening tests for druggable variants. In addition, NGS has some limitations, which are often restricting its use to the context of research programs.

As compared to de novo AML, some gene mutations could be more frequent in t-AML patients (*TP53* [36%], *PTPN11* [12%], *NRAS* [10%], *KRAS* [5%]), equally frequent (*IDH1* [10%], *IDH2* [10%]), or less frequent (*FLT3* [7%], *DNMT3A* [7%]) (Ok et al. 2015a).

No differences have been reported regarding morphological and immunophenotypic characterization between t-APL and de novo APL (Duffield et al. 2012). To diagnose t-APL, demonstration of the t(15;17) or *PML/RARA* rearrangement is also mandatory. Some studies suggested that patients developing t-APL after mitoxantrone show a higher prevalence of long-type (bcr 1) *PML/RARA* isoform due to a specific DNA-break hotspot in the *PML* gene (Hasan et al. 2008). However, this has not been confirmed later (Kayser et al. 2017). It is expected that NGS studies will help to elucidate the genetic features of t-APL and the potential differences with de novo APL (Lo-Coco et al. 2013).

4.6 Classification

According to the WHO 2016 classification, patients diagnosed with AML diagnosed after receiving cytotoxic drugs, radiation therapy, or immunosuppressive agents for neoplastic and non-neoplastic diseases should be classified in the t-MN group (Arber et al. 2016; Döhner et al. 2017). However, this designation includes also patients diagnosed with MDS or MDS/MPN after mutagenic therapy, so t-AML seems to be a better term to differentiate AML from other t-MN diseases (Kayser et al. 2017). According to the WHO 2016, if a recurrent genetic abnormality is diagnosed, this should be added to the nomenclature (see Table 4.2). It remains controversial whether well-defined entities with particular treatment approaches and prognosis, such as APL or core-binding-factor (CBF) AML, should be included in the t-MN cluster, as recommended by WHO, or could preferably remain in their respective groups of recurrent genetic abnormalities.

The 2016 WHO AML with myelodysplasia-related changes (MRC-AML) is a wide entity that encompasses both sAML and de novo AML. The WHO 2001 defined AML with multilineage dysplasia (AML-MLD) as a new category, which was only defined by the presence of ≥50% dysplastic abnormalities in ≥2 hematopoietic cell lines. The AML-MLD was replaced by the MRC-AML in the WHO 2008 revision since several studies showed that MLD was not an independent factor when cytogenetics was incorporated into the prognostic models (Vardiman et al. 2009). With hindsight, more authors have insinuated the lack of prognostic significance of MLD (Miesner et al. 2010).

The WHO 2008 AML-MRC is defined as AML (≥20% blasts of bone marrow [BM] or peripheral blood [PB]) with at least one of the following criteria: (1) ≥50% dysplastic abnormalities in ≥2 hematopoietic cell lines (MLD); (2) prior history of MDS or MDS/MPN; and (3) MDS-related cytogenetic abnormalities and absence of recurrent genetic abnormalities.

Regarding MLD assessment, these are the current recommendations by WHO:

Table 4.2 sAML classification according to antecedents, RGA, and WHO 2016

Antecedents	RGA	WHO 2016 classification	sAML
Previous therapy (unrelated disease)	No	t-MN	Yes
	Yes	t-MN with RGA	Yes
Previous history of MDS or MDS/MPN[a]	No	MRC-AML	Yes
	Yes	AML with RGA	Yes
Myelodysplasia-related cytogenetic abnormality[a]	No	MRC-AML	No
• Complex karyotype: ≥3 unrelated abnormalities (not including the recurrent genetic abnormalities encountered in AML) • Unbalanced abnormalities: – −7/del(7q) – del(5q)/t(5q) – i(17q)/t(17p) – −13/del(13q) – del(11q) – del(12p)/t(12p) – Idic(X)(q13) • Balanced abnormalities: – t(11;16)(q23.3;p13.3) – t(3;21)(q26.2;q22.1) – t(1;3)(p36.3;q21.2) – t(2;11)(p21;q23.3) – t(5;12)(q32;p13.2) – t(5;7)(q32;q11.2) – t(5;17)(q32;p13.2) – t(5;10)(q32;q21.2) – t(3;5)(q25.3;q35.1)	Yes	AML with RGA	No
Multilineage dysplasia[a]	No	MRC-AML	No
• Dysgranulopoiesis, dyserythropoiesis, and/or dysmegakaryopoiesis (>50% in ≥2 cell lineages)	Yes	AML with RGA	No

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MDS/MPN* myelodysplastic syndrome/myeloproliferative neoplasm, *MRC-AML* acute myeloid leukemia with myelodysplasia-related changes, *RGA* recurrent genetic abnormalities, *sAML* secondary acute myeloid leukemia, *t-MN* therapy-related myeloid neoplasms, *WHO* World Health Organization

[a]Absence of prior mutagenic therapy for unrelated disease. Recurrent genetic abnormalities (RGA): t(8;21)(q22;q22.1); *RUNX1-RUNX1T1;* inv.(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11; PML-RARA;* t(9;11)(p21.3;q23.3); *MLLT3-KMT2A;* t(6;9)(p23;q34.1); *DEK-NUP214;* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM;*t(1;22)(p13.3;q13.3); *RBM15-MKL1*; Mutated *NPM1;* Biallelic mutations of *CEBPA*

- Dysgranulopoiesis: 25–100 neutrophils—hypogranular cytoplasm, hyposegmented nuclei or bizarrely segmented nuclei, cytoplasmic vacuoles—myeloperoxidase deficiency (50%, 20 cells)
- Dyserythropoiesis: at least 25 mature erythroblasts—megaloblastosis, karyorrhexis and nuclear irregularity, fragmentation or multinucleation—ring sideroblasts, PAS positivity
- Dysmegakaryopoiesis: at least six megakaryocytes—micromegakaryocytes, normal sized, or large megakaryocytes with non-lobulated or multiple nuclei

According to the WHO 2016 update, patients diagnosed with MRC-AML must meet at least one of the following criteria (along with the absence of both prior cytotoxic therapy for unrelated disease and recurrent genetic abnormalities [RGA]):

- Previous history of MDS or MDS/MPN
- Myelodysplasia-related cytogenetic abnormality (see Table 4.2)
- Multilineage dysplasia (see Table 4.2)

Thus, AML patients with a medical history of hematologic disorder who have received therapy for any unrelated disease or show any RGA should not be classified as MRC-AML. Table 4.2 shows detailed information regarding sAML classification according to antecedent disorders, presence of RGA, and WHO 2016 terminology.

Although the WHO pathological classification attempts to define biologically homogeneous entities with similar prognosis, the WHO definitions should be used together with age, performance status (PS), cytogenetics, and molecular profile in order to decide the best available regimen for each entity and patient (Hulegårdh et al. 2015; Juliusson et al. 2009; Nilsson et al. 2019).

4.7 Prognosis

Similar to de novo AML patients, the prognosis of sAML patients is related to several factors as age, PS, cytogenetics, and molecular profile (Fig. 4.1) (Wheatley et al. 2009). However, sAML patients are often older, with worse PS and genetic features, so they tend to be more frequently considered unfit for intensive chemotherapy. Other baseline characteristics, such as WBC counts, previous comorbidities, or response to induction treatment, have been also associated with worse prognosis in AML (Wheatley et al. 2009; Schoch et al. 2004). It is expected that sAML patients could present with more comorbidities, since prior treatments or malignant dis-

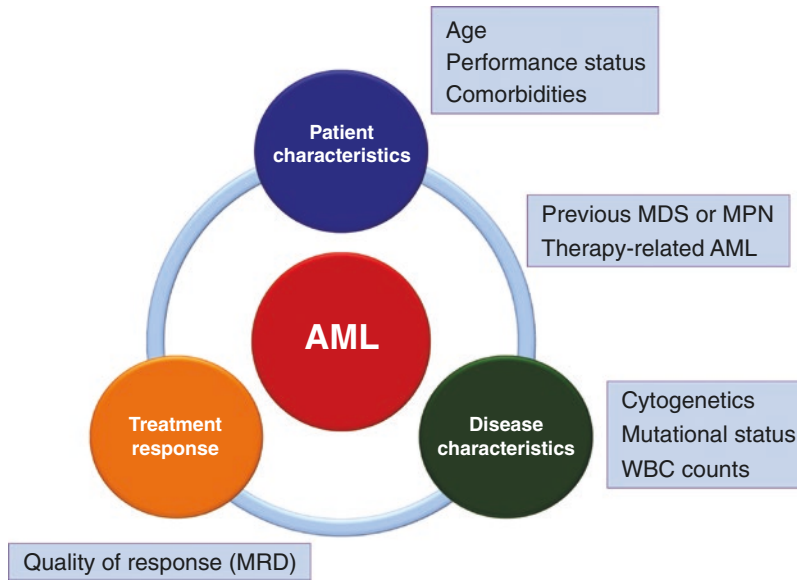

Fig. 4.1 Main prognostic factors in AML: the place of sAML (MDS-MPN-AML and t-AML), between patient factors and disease-related factors

orders could have caused sequelae (e.g., other organ damage, low hematopoietic stem cell reserve, persistence of malignant disease). In addition, the prognostic impact of some well-established gene mutations in sAML is unclear (e.g., *FLT3*, *NPM1*), as available data mainly derive from studies performed in de novo AML patients with normal karyotype.

The dilemma about considering sAML as an independent prognostic factor remains unsolved as published manuscripts revealed discrepant results (Juliusson et al. 2009; Wheatley et al. 2009; Fröhling et al. 2006b; Szotkowski et al. 2010). Some studies have shown a different prognosis depending on the type of sAML: MPN patients who develop a leukemic transformation show the worst clinical outcomes, with a median survival between 6–11 months and 1-year OS of 10%, which is worse than 20% in t-AML, 41% in de novo AML, and 43% in AML from MDS (Østgård et al. 2015; Mesa et al. 2005; Thepot et al. 2010). As in de novo AML, molecular and cytogenetic changes play a relevant role in establishing the prognosis of sAML. t-AML patients with CBF have a longer OS than those with intermediate and adverse genetic risk, but prognosis seems to be worse than in de novo CBF AML patients (Borthakur et al. 2009). Mutations and loss of heterozygosity of *TP53,* which have been identified as independent negative prognostic factors for OS, are common in sAML (reported in 17–37% of t-MN patients) (Christiansen et al. 2001; Ok et al. 2015b). Similarly, shorter OS has also been observed in t-MN patients with amplification of the *MLL* gene, compared with patients without these mutations (Andersen et al. 2001). Table 4.3 shows the main studies analyzing the prognostic factors in sAML.

Unlike t-MN, the prognosis of t-APL is favorable with anthracycline-based chemotherapy plus all-trans-retinoic acid (ATRA) or ATRA plus arsenic trioxide (ATO). Several studies showed a similar prognosis as compared to de novo APL, particularly after adjusting by age and PS (Ammatuna et al. 2011; Dayyani et al. 2011; Lo-Coco et al. 2013).

Table 4.3 Prognostic factors in studies performed in sAML patients

Author (Year) [Reference]	Characteristics	Prognostic factors: findings
Juliusson et al. (2009)	Registry All AML *N* = 2767 Intensive treatment: 62%	PS III-IV: Higher ED in all ages
		Intensive treatment: Improves ED rates and OS
		sAML: No differences between de novo and sAML in ED at the same age
Østgård et al. (2010)	Registry All AML *N* = 630 (sAML: 157 [25%]; de novo: 473 [75%]) Intensive treatment: 58%	Age ≥ 60 (CR, OS, and DFS): More sAML patients ≥60 yo did not receive curative treatment
		PS (OS)
		Unfavorable cytogenetics (CR, OS, and DFS): MDS-AML (34%) > t-AML plus MPN-AML (20%)
		To achieve CR: • Age • Treatment protocol • Cytogenetics
		sAML patients in CR: Similar DFS than de novo
		CR, OS, and DFS: When correcting for age, cytogenetics, PS, and WBC, sAML lost prognostic significance

(continued)

Table 4.3 (continued)

Author (Year) [Reference]	Characteristics	Prognostic factors: findings
Schoch et al. (2004)	Retrospective *N* = 1184 (t-AML: 93 [8%]; de novo: 1091 [92%]) Intensive treatment: 100%	Favorable cytogenetics: Better OS (independent of age and WBC)
		Unfavorable cytogenetics: • Worse OS (independent of age and WBC) • More adverse cytogenetics in t-AML (46%) than in de novo AML (20%), but the same abnormalities
		Age: • For OS (t-AML + de novo) • No impact for OS in t-AML group
		WBC: • For OS (t-AML + de novo) • No impact for OS in t-AML group
Kayser et al. (2011)	Prospective *N* = 2853 (t-AML: 200 [7%]; de novo: 2653 [93%]) Intensive treatment: 100%	t-AML: • An adverse prognostic factor for death in CR in young intensive pts. (not for relapse) → cumulative toxicity of treatments • An adverse prognostic factor for relapse old pts (not for death in CR) → lower dose in elderly • An adverse prognostic factor for OS in young intensive pts • Similar rates of CR in both groups (sAML and de novo), refractory disease and ED (differences by age)
Hulegårdh et al. (2015)	Registry *N* = 3363 (AHD-AML: 630 [18.7%]; t-AML: 259 [7.7%]; de novo: 2474 [73.6%]) Intensive treatment: 58%	De novo vs sAML: Different age, gender, and cytogenetics • sAML: Impact in OS in young patients (no impact on elderly) • sAML: Worse OS than de novo in all cytogenetic groups (sAML independent of karyotype) • AHD-AML and t-AML independently associated to poor OS • AHD-AML: Worse PS than t-AML • AHD-AML: Low-risk cytogenetics is uncommon • High-risk cytogenetics: t-AML (46%) >AHD-AML (40%) > de novo (26%) • Worse CR and OS in t-AML and MRC-AML vs de novo, regardless of PS
Østgård et al. (2015)	Registry	Response to therapy (prognostic factor for OS) Prognostic factor for OS: Cytogenetic group and type of sAML • MDS-AML no impact on OS (dismal outcomes) • t-AML: Higher frequency of adverse risk • OS in intermediate risk: t-AML similar to MPN-AML < de novo AML • 1-year OS in adverse risk: MPN-AML (10%), t-AML (20%), de novo AML (41%), MDS-AML (43%) • MDS-AML and t-AML impact on OS: – <60 yo: Worse OS – (≥60 yo: Longer OS • MPN-AML: Worse OS than MDS-AML (age- and ctyogenetics-independent) • Less HSCT in MPN-AML and t-AML due to lower CR rate, higher induction death, older age, more comorbidities, and worse PS)
Szotkowski et al. (2010)	Retrospective *N* = 574 Intensive treatment: 66%	sAML: Unfavorable for younger and older than 60 years Intensive treatment according to type of AML: • sAML: 69 (48% of sAML) • De novo: 307 (71% of de novo AML)

Table 4.3 (continued)

Author (Year) [Reference]	Characteristics	Prognostic factors: findings
Zeichner and Arellano (2015)	Retrospective De novo AML sAML	ECOG >2 is unfavorable in AML (including sAML) Higher risk of induction death → require less intensive therapy
Armand et al. (2007)	Retrospective *N* = 556 (t-MN: 80 [14%]; AML or MDS: 476 [16%]) Previous HSCT	Cytogenetics • OS and DFS in t-MN: Favorable > unfavorable • After stratifying by cytogenetics: No differences between de novo and t-MN
Christiansen et al. (2001)	Retrospective *N* = 77 (t-MN/t-MDS: 52 [68%]; t-AML: 25 [32%]) Treatment: NA	Mutations of *p53* were significantly associated with: • Deletion or loss of 5q • Complex karyotype • Old patients • Extremely poor prognosis
Ok et al. (2015b)	Retrospective *N* = 108 (t-MN/t-MDS: 53 [49%]; t-AML: 55 [51%]) Treatment: NA	Loss of heterozygosity of *TP53*: Worse OS
Andersen et al. (2001)	Retrospective *N* = 70 t-MN Treatment: NA	Amplification of the *MLL* gene significantly associated with: • Deletion or loss of 5q • Complex karyotype • Old patients • Alkylating agents • Worse OS
Borthakur et al. (2009)	Retrospective *N* = 188 CBF-AML (sAML: 17 [9%]; de novo: 171 [91%]) Intensive treatment: 100%	CBF sAML: Worse OS and EFS than CBF de novo AML (but only after matched-analysis by age, ECOG, and the presence of additional chromosomal abnormalities)
Fröhling et al. (2006b)	Retrospective *N* = 361 (sAML: 119 [33%]; de novo: 242 [67%]) Age ≥ 60 yo Intensive treatment: 100%	sAML no impact Independent impact on OS: • Age • Cytogenetics
Wheatley et al. (2009)	Retrospective *N* = 2483 (sAML: 544 [22%]; de novo: 1939 [78%]) Age ≥ 60 yo Intensive treatment: 100%	Independent impact on OS: • Age • sAML • WBC • PS • Cytogenetics
Stölzel et al. (2011)	Retrospective sAML *N* = 305 (MDS-AML: 233 [76%]; t-AML: 72 [24%]) Intensive treatment: 100%	Age (OS and EFS) Cytogenetic risk (OS) Platelets count (OS and EFS) NPM1 positivity (OS and EFS) Type of sAML was not a prognostic factor
Thepot et al. (2010)	Retrospective *N* = 54 (MPN-AML: 26 [48%]; MPN-MDS: 28 [52%]) Azacitidine	For CR: • Underlying MPN: 14% CR for PV vs 43% for ET • WHO classification at diagnosis: 36% CR in MDS vs 12% in AML

AHD-AML acute myeloid leukemia with an antecedent hematological disease, *AML* acute myeloid leukemia, *CBF* core binding factor, *CR* complete remission, *DFS* disease-free survival, *ECOG* Eastern Cooperative Oncology Group score, *ED* early death, *EFS* event-free survival, *ET* essential thrombocythemia, *HSCT* hematopoietic stem cell transplantation, *MDS-AML* AML after myelodysplastic syndrome, *MPN-AML* AML after myeloproliferative neoplasm, *MRC-AML* AML with myelodysplasia-related changes, *NA* not available, *OS* overall survival, *PV* polycythemia vera, *PS* performance status, *pts* patients, *sAML* secondary AML, *t-AML* therapy-related AML, *t-MDS* therapy-related myeloproliferative neoplasm, *t-MN* therapy-related myeloid neoplasm, *WBC* white blood cell, *yo* years old

4.8 Treatment

The optimal treatment options for sAML patients are not yet established. This therapeutic dilemma comes from the lack of well-designed studies in this subset of patients, as they are commonly excluded from trials and protocols (Juliusson et al. 2009; Mengis et al. 2003).

Despite new advances, front-line therapy remains a challenge in sAML. In addition to older age and worse PS of these patients, deteriorated baseline characteristics because of the preceding treatments or concomitant malignant disease activity must be taken into account to judge the best approach for each patient. As in de novo AML, genetic and molecular characterization is mandatory for the initial risk-assessment of sAML patients, which can be categorized in favorable, intermediate, and adverse groups. Although, in general, we can recommend that sAML patients should receive similar treatment as de novo AML, specific characteristics of sAML patients may justify a distinct approach in some instances. Table 4.4 shows detailed information on studies who analyzed treatment outcomes in sAML.

4.8.1 Younger Patients

As in young patients with de novo AML, induction therapy in sAML is based on intensive 3 + 7 chemotherapy, with a combination of cytarabine for 7 days plus an anthracycline for 3 days, usually idarubicin or daunorubicin. Nevertheless, other schedules have also been explored (Döhner et al. 2017; Fey and Buske 2013; Tallman et al. 2019; De Kouchkovsky and Abdul-Hay 2016; Lee et al. 2011; Burnett et al. 2013; Zeidner et al. 2015; Stone et al. 2015; Lee et al. 2017; Holowiecki et al. 2012; Burnett et al. 2015). Due to the high risk of relapse, the majority of sAML fit patients achieving a first complete remission (CR) will be candidates to receive an allogeneic hematopoietic stem cell transplantation (HSCT). In consequence, an early search for a suitable donor should be started at diagnosis. After achieving CR, consolidation cycles with high-dose cytarabine-based schedules are recommended for patients with optimal PS and favorable cytogenetic risk. In contrast, the preferred strategy to achieve long-term survival in patients with intermediate-risk genetics is to perform an allogeneic HSCT (De Kouchkovsky and Abdul-Hay 2016; Li et al. 2018; Sengsayadeth et al. 2018; Litzow et al. 2010; Yakoub-Agha et al. 2000). Unfortunately, the prognosis in patients with poor-risk cytogenetics is dismal, regardless of the treatment administered. Despite this, allogeneic HSCT remains the most appropriate post-remission modality for patients with high-risk cytogenetics sAML, especially in younger patients with good PS (Sengsayadeth et al. 2018; Kennedy et al. 2013). Few data have been published comparing patients with or without HSCT after induction therapy in sAML patients. Although treatment-related mortality and toxicity after allogeneic HSCT is suspected to be higher in sAML patients than in de novo AML, allogeneic HSCT improves survival and is considered the only realistic curative option in patients with sAML (Nilsson et al. 2019).

In younger patients who are considered unfit for intensive schedules (e.g., because of another active malignancy or end-organ failure), front-line approaches using hypomethylating agents (HMAs) could prolong OS (Zeichner and Arellano 2015).

As a general recommendation, participating in clinical trials should be the preferred option for all sAML patients (Fey and Buske 2013; Tallman et al. 2019).

4.8.2 Older Patients

Older patients (especially those aged more than 70–75 years) are usually considered unfit and often receive non-curative schemes or supportive care exclusively. Intensive therapies in older patients are limited to those with optimal PS, and considered able to withstand very toxic schedules (Löwenberg et al. 1998; Anderson et al. 2002). In the last decades, through a more accurate risk stratification of patients and improvements in supportive therapy, intensive schedules have also

Table 4.4 Studies of induction therapy in secondary AML patients

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Registries and observational studies							
Schoch et al. (2004)	Registry AML t-AML	Intensive chemotherapy	93 t-AML 1091 de novo	57 (16–82) 58 (16–84)	No differences in the CR rate	t-AML:10 m De novo: 15 m (p = 0.0007)	See Table 4.3
Hulegårdh et al. (2015)	Registry Age ≥ 17 yo AML APL	AML: IDA + Ara-C (3 + 7) APL: ATRA + IDA/DNR BSC Intensive: 1967 (58%) Non-intensive: 1396 (42%)	3363 De novo AML: 2474 (74%) AHD-AML: 630 (19%) t-AML: 259 (8%) <65 yo: 1165 (35%) ≥65 yo: 2198 (65%)	De novo: 70 (17–98) AHD-AML: 73 t-AML: 70	IDA + Ara-C (3 + 7): <65 yo • De novo: CR 82% • AHD-AML: CR 43% • t-AML: CR 56% IDA + Ara-C (3 + 7): ≥65 yo • De novo: CR 59% • AHD-AML: CR 37% • t-AML: CR 53% Non-intensive <65 yo • De novo: CR 11% • AHD-AML: CR 7% • t-AML: CR 0% Non-intensive ≥65 yo • De novo: CR 3% • AHD-AML: CR 1% • t-AML: CR 3%	IDA + Ara-C (3 + 7): <65 yo • De novo: ~3 y • AHD-AML: < 1 y • t-AML: ~1 y Patients <65 yo + sAML: Similar mOS to elderly patients with sAML	• De novo: Higher CR in younger • sAML: Similar CR rates in younger and older

(continued)

Table 4.4 (continued)

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Østgård et al. (2015)	Registry Age ≥ 15 yo Non-APL	Intensive CHT: 1567 (51%) • DNR + Ara-C (3 + 7): 41% • IDA + Ara-C (3 + 7): 35% • MIT + Ara-C (3 + 7): 18%	3205 De novo AML: 2249 (74%) MDS-AML: 350 (11%) MPN-AML: 253 (8%) t-AML: 203 (7%)	Intensive CHT: De novo: 58 (15–86) MDS-AML: 64 (18–82) MPN-AML: 62 (38–87) t-AML: 58 (22–76)	Intensive CHT: De novo: CR 75% MDS-AML: CR 59% MPN-AML: CR 54% t-AML: CR 61%	OS 1- and 3y (intensive CHT): • De novo: 65%, 39% • t-AML: 45%, 24% • Non-MDS-sAML: 31%, 11%	See Table 4.3
Østgård et al. (2010)	RETROSP Age ≥ 15 yo AML (includes APL)	Anthracycline + Ara-C (intensive): 364 (58%)	630 AML 157 sAML (25%)	Intensive: 58 sAML: 69 De novo: 66	sAML: CR 56% De novo: CR 73%	Intensive: 13 m sAML: 5.7 m De novo: 16 m	See Table 4.3
Szotkowski et al. (2010)	RETROSP Age ≥ 18 yo AML APL	Intensive treatment: De novo: 305 (71%) sAML: 69 (48%)	574 De novo AML: 430 (75%) MDS-AML: 86 (15%) t-AML: 58 (10%)	De novo: 58 (18–80) sAML: 64 (20–87) Intensive CHT: De novo: 53 (18–80) sAML: 55 (20–76)	Intensive CHT: De novo: CR 73% sAML: CR 46%	Intensive CHT: Shorter OS in sAML than de novo ($p < 0001$)	See Table 4.3
Mesa et al. (2005)	RETROSP MPN-AML	AML-like CHT: 24 (26%) Non-intensive: 19 (21%) BSC: 48 (53%)	91	66 (41–82)	AML-like: CR 0% (41% reverted into chronic-phase, TRM 33%)	2.6 m (all patients) AML-like OS: 3.9 m Non-intensive CHT: 2.9 m BSC: 2.1 m	2 patients alive after 41 and 57 m with either cytarabine-based induction CHT or HSCT

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Nilsson et al. (2019)	RETROSP AML sAML	Intensive treatment (100%)	3337 De novo: 2613 (78%) AHD-AML: 442 (13%) t-AML: 282 (8%) HSCT: • De novo: 576 (17%) • AHD-AML: 74 (17%) • t-AML: 57 (20%)	HSCT: • De novo: 48 (17–72) • AHD-AML: 58 (28–77) • t-AML: 51 (18–68) No HSCT: • De novo: 64 (17–86) • AHD–AML: 68 (24–83) • t-AML: 66 (34–83)	De novo: CR 72% AHD-AML: CR 45% t-AML: CR 60%	HSCT OS 3 y, 5 y: • De novo: 55%, 40% • MDS-AML: 31%, 18% • MPN-AML: 37%, 32% • t-AML: 42%, 25% No HSCT OS 3 y, 5 y: • De novo: 24%, 16% • MDS-AML: 5%, 2% • MPN-AML: 3%, 0% • t-AML: 21%, 10%	NA
Li et al. (2018)	RETROSP sAML	Haplo-HSCT: Myeloablative conditioning: 57 (38%) RIC: 97 (62%)	154 At HSCT: CR 69; active sAML 85	60 (at HSCT)	Not applicable	OS 2 y: 43%	LFS 2 y: 37%
Yakoub-Agha et al. (2000)	RETROSP t-MDS t-AML	Allo-HSCT	70 t-MDS: 31 t-AML: 39 At HSCT: CR 24; active 46	37 (16–55)	Not applicable	OS 2 y: 30%	EFS 2 y: 28% TRM 2 y: 49% Relapse 2 y: 42%
Litzow et al. (2010)	RETROSP t-MDS t-AML	Allo-HSCT Myeloablative conditioning: 670 (77%) RIC: 198 (23%)	868 t-MDS: 323 (37%) t-AML: 545 (63%) At HSCT: CR 317 (37%); Active 551 (63%) (t-AML: 228; t-MDS: 323)	40 (4–72)	Not applicable	OS 1 y, 5 y: 37%, 22%	DFS 1 y, 5 y: 32%, 21% TRM 1 y, 5 y: 41%, 48% Relapse 1 y, 5 y: 27%, 31%

(continued)

Table 4.4 (continued)

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Sengsayadeth et al. (2018)	RETROSP sAML	Allo-HSCT	4997	58 (at HSCT)	Not applicable	OS 2 y: 45%	DFS 2 y: 39% NRM 2 y: 28% Inferior OS and DFS: • Active disease • Poor-risk cytogenetics • Older age • Lower ECOG • Hematologic malignancies
Kennedy et al. (2013)	MPN-AML	Curative intent: CHT ± Allo-HSCT BSC (CHT = 3 + 7 or MIT + ETOP+HiDAC)	75 CHT ± Allo-HSCT: 39 (52%) BSC: 36 (48%)	65 (36–89) CHT ± Allo-HSCT: 57 (36–88) BSC: 72 (54–89)	CHT ± Allo-HSCT: CR: 18 (46%) → Allo-HSCT in 17	6.6 m CHT ± Allo-HSCT: 9.4 m BSC: 2.3 m	All: OS 2 y: 15% CHT ± Allo-HSCT: OS 2 y: 26% CHT + Allo-HSCT: OS 2 y: 47% CHT: OS 2 y: 15% BSC: OS 2 y: 3%
Thepot et al. (2010)	MPN-AML MPN-MDS	Azacitidine	54 MPN-AML: 26 (48%) MPN-MDS: 28 (52%)	69.5 (37–89)	MPN-AML CR: 12% MPN-MDS CR: 36%	11 m (all patients) MPN-AML OS: 8 m MPN-MDS OS: 14 m	NA
Borthakur et al. (2009)	CBF-AML	Intermediate-dose to high-dose cytarabine-based CHT	*N* = 188 CBF-AML (sAML: 17 [9%]; De novo: 171 [91%])	sAML: 62 (31–75) De novo: 61 (31–73)	CR + CRp: 92%	CBF-AML OS: 62 m sAML OS: 23 m De novo OS: 143 m	See Table 4.3
Dumas et al. (2017)	RETROSP sAML (MDS-AML: 69 [37.5%]; MPN-AML: 32 [17.4%]; t-AML: 83 [45%])	Intensive CHT Azacitidine	199 Intensive CHT: 92 (46%) Azacitidine: 107 (54%)	Intensive CHT: 66 (IQR: 63–71) Azacitidine: 76 (IQR: 71–80)	CR + CRi: Intensive: 58 (63%) Azacitidine: 21 (20%)	Intensive mOS: 9.6 m Azacitidine mOS: 10.8 m ($p = 0.899$)	Azacitidine versus intensive CHT: OS was not significantly different according to AML subtypes

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Acute promyelocytic leukemia							
Kayser et al. (2017)	RETROSP t-APL	ATRA+CHT (intensive) ATO + ATRA (intensive) ATO + ATRA + CHT (intensive) ATRA alone	103 ATRA + CHT: 53 (51.5%) ATO + ATRA: 24 (23.3%) ATO + ATRA + CHT: 19 (18.4%) ATRA: 7 (6.8%)	59 (18–80)	ATRA + CHT: ED 12%, CR 78% ATO + ATRA: ED 0%, CR 100% ATO + ATRA + CHT: ED 5%, CR 95% ATRA alone: ED 43%, CR 57%	3.7 y OS 2 y (intensive): 88% ATRA + CHT: OS 2 y 84% ATO + ATRA: OS 2 y 89% ATO + ATRA + CHT: OS 2 y 95%	EFS 2 y (intensive): 84% RFS 2 y (intensive): 84% ATRA+CHT: EFS 2 y 78%, RFS 2 y 78% ATO + ATRA: 2 y EFS 89%, RFS 2 y 90% ATO + ATRA + CHT: 2 y EFS 95%, RFS 2 y 95% EFS 2 y (censoring died patients due to primary malignancy): ATO-based 95%, ATRA + CHT 78% ($p = 0.042$)
Elliott et al. (2012)		ATRA+CHT	64 (11 t-APL)	56 (18–80)	sAPL: CR 64% (RES 0%) De novo APL: CR 92% (RES 0%)	sAPL: OS 51% De novo APL: 84%	NA
Beaumont et al. (2003)	RETROSP t-APL	Anthracycline + Ara-C ATRA + CHT	106	55 (12–82)	Anthracycline + Ara-C CR: 87% (ED: 13%) ATRA + CHT: CR 80% (ED: 20%)	OS 5 y: 59%	OS 8y: • After CHT alone: 68% • After RT alone: 59% • Both: 52%
Pulsoni et al. (2002)	RETROSP sAPL (secondary)	AIDA (31 sAPL; 641 de novo)	692 (51 sAPL)	sAPL: 57 (27–76) De novo: 39 (1–74)	sAPL CR: 97% De novo CR: 68%	sAPL OS 4 y: 65% De novo OS 4 y: 78%	sAPL EFS 4 y: 93% De novo EFS 4 y: 85%

(continued)

Table 4.4 (continued)

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Dayyani et al. (2011)	RETROSP t-APL	ATRA+CHT ATO + ATRA	29 both arms ATRA + CHT: 10 ATO + ATRA: 19	ATRA+CHT: 54 (35–75) ATO + ATRA: 53 (36–81)	ATRA+CHT: CR 70 ATO + ATRA: CR 89 ($p = 0.35$)	ATRA+CHT: mOS 171 w; ATO + ATRA: mOS not achieved ($p = 0.79$)	NA
Clinical trials							
Löwenberg et al. (1998)	RCT, PROSP, phase-III	Ara-C (100 mg/m^2 d: 1–7) + DNR (30 mg/m^2 d: 1–3) or Ara-C (100 mg/m^2 d: 1–7) + MIT (8 mg/m^2 d: 1–3)	63 61 124 both arms	68 (60–88) in both arms	Mixing 2 arms: CR: 46 (37) vs AML de novo CR: 207 (44); $p = 0.21$	Mixing 2 arms: OS sAML vs AML 1st **$p = 0.02$**	NA
Anderson et al. (2002)	RCT, PROSP, Phase-III	Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) or MIT (10 mg/m^2 d: 1–5) + ETOP (100 mg/m^2 d: 1–5)	36 38 Both: 74	68 (56–84) 67 (56–86)	Mixing 2 arms: CR: 19 (26) vs AML de novo CR: 107 (42); $p = 0.011$	Mixing 2 arms: OS 2 y: 7 (10) vs AML de novo OS 2 y: 41 (16); $p = 0.11$	Mixing 2 arms: RFS 2 y: 8 (11) vs AML de novo RFS 2 y: 46 (18) $P = 0.89$
Löwenberg et al. (2009)	RCT, PROSP	Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) or Ara-C (200 mg/m^2 d: 1–7) + DNR (90 mg/m^2 d: 1–3) Both arms 2° cycle: Ara-C (1000 mg/m^2 d: 1–6)	75 MDS-AML: 52 t-AML: 23 94 MDS-AML: 67 t-AML: 27 169 both arms MDS-AML: 119 t-AML: 50	68 (60–79) 68 (60–83)	Mixing 2 arms: CR: 80 (47) MDS-AML: CR: 54 (45) t-AML: CR: 26 (52) vs AML de novo CR: 399 (62); $p < 0.001$	OS 2 y: 37 (22) MDS-AML: CR: 54 (45) t-AML: CR: 26 (52) vs AML de novo OS 2 y: 193 (30); $p = 0.01$	EFS 2 y: 19 (11) MDS-AML: EFS 2 y: 11 (9) t-AML: EFS 2 y: 8 (16) vs AML de novo EFS 2 y: 129 (20); $p = 0.003$ DFS 2 y: 36 (21) MDS-AML: DFS 2 y: 21 (18) t-AML: DFS 2 y: 15 (30) vs AML de novo DFS 2 y: 200 (31); $p = 0.27$

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Chauncey et al. (2010)	RCT, PROSP, Phase-II, 2-Arms	Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) or Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) + CSA (loading dose of 6 mg/kg over 2 h and 16 mg/kg CI d: 1–3)	16 MDS-AML: 14 t-AML: 2 7 MDS-AML: 7 t-AML: 0	68 (56–85) 65 (56–81)	CR: 1 (6) MDS-AML: CR: 0 (0) t-AML: CR: 1 (50) CR: 2 (29) MDS-AML: CR: 2 (29) t-AML: Not applicable	NA	NA
Röllig et al. (2010)	RCT, PROSP, 1-Arm	Ara-C (100 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3)	236	67 (61–87)	CR: 100 (42) vs AML de novo CR: 354 (53); ***p* = 0.007**	mOS 8.4 m OS 3 y: 27 (11.4) OS 5 y: 12 (5.2) vs AML 1st L, ***p* = 0.016**	mDFS 8.5 m DFS 3 y: 21 (8.8) DFS 5 y: 16 (6.6)
Lee et al. (2011)	RCT, PROSP, Phase-III MDS-AML	Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) or Ara-C (200 mg/m^2 d: 1–7) + DNR (90 mg/m^2 d: 1–3)	6 11 17 both arms	43 (15–60) in both arms	Mixing 2 arms: CR: 10 (59) vs AML de novo CR: 286 (78); $p = 0.063$	Mixing 2 arms: OS at 5 y: 2 (14.1) vs AML de novo OS at 5 y: 153 (41.8); ***p* = 0.009**	Mixing 2 arms: EFS 5 y: 4 (23.5) RFS 5 y: 7 (40) vs AML de novo EFS 5 y: (40.8) RFS 5 y: 129 (35) $p = 0.056$; 0.307
Holowiecki et al. (2012)	RCT, PROSP, Phase-III MDS-AML	Ara-C (200 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) or 2-CdA (5 mg/m^2 d: 1–5) + DNR (60 mg/m^2 d: 1–3) or FLU (25 mg/m^2 d: 1–5) + DNR (60 mg/m^2 d: 1–3)	22 20 27	48 (18–60) 47 (17–60) 47 (18–60)	NA	OS at 3 y: 3 (12) OS at 3 y: 4 (20) OS at 3 y: 6 (22) $p = 0.94$	NA

(continued)

Table 4.4 (continued)

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Burnett et al. (2013)	RCT, PROSP, 2-Arms	Ara-C (100 mg/m^2 d: 1–7) + DNR (50 mg/m^2 d: 1–3) or Ara-C (100 mg/m^2 d: 1–7) + DNR (50 mg/m^2 d: 1–3) + ETOP (100 mg/m^2 d: 1–5)	88 84	53 (16–72) 53 (16–72)	NA	OS 5 y: 22 (25) OS 5 y: 17 (20.2)	NA
Lancet et al. (2014)	RCT, PROSP, Phase-II, 2-Arms	Ara-C (100 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) or CPX-351 (100 units/m^2 d: 1, 3, 5)	19 33	68 (61–77) 68 (60–77)	CR: 6 (32) CR: 12 (58) $p = 0.06$	6.1 m 12.1 m **$p = 0.01$**	mEFS, 1.3 m mEFS, 4.5 m $p = 0.08$
Burnett et al. (2015)	RCT, PROSP, 2-Arms	Ara-C (100 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) or Ara-C (100 mg/m^2 d: 1–7) + DNR (90 mg/m^2 d: 1–3)	58 59	53 (16–72) 53 (16–72)	NA	OS 2 y: 34 (58.6) OS 2 y: 29 (49.2)	NA
Müller-Tidow et al. (2016)	RCT, PROSP, 2-Arms	Ara-C (100 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) or Ara-C (100 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) + Azacitidine (75 mg/m^2 d: −5 to 1)	32 30	69 (all ≥61) 70 (all ≥61)	NA	OS 2 y: 16 (50) OS 2 y: 10 (33.3) **$p = 0.048$**	EFS: 7 (21.9) EFS: 5 (16.7) $p = 0.627$

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Zeidner et al. (2015)	RCT, PROSP, Phase-II, 2-Arms	Ara-C (100 mg/m^2 d: 1–7) + DNR (90 mg/m^2 d: 1–3) or FLAM: Flavopiridol (50 mg/m^2 d: 1–3) + Ara-C (667 mg/m^2 CI d: 6–8) + MIT (40 mg/m^2 d: 9)	26 52	60 (22–69) 59 (19–70)	CR: 9 (35) CR: 31 (60)	NA	NA
Stone et al. (2015)	RCT, PROSP, Phase-III	Ara-C (200 mg/m^2 d: 1–7) + DNR (45 mg/m^2 d: 1–3) or Ara-C (200 mg/m^2 d: 1–7) + Amonafide (60 mg/m^2 d: 1–5)	217 MDS-AML: 104 t-AML: 88 t-AML-MDS: 24 216 MDS-AML: 111 t-AML: 85 t-AML-MDS: 20	63 (27–83) 65 (19–84)	CR: 97 (45) MDS-AML: CR: 43 (41) t-AML: CR: 49 (56) t-AML-MDS: CR: 7 (29) CR: 99 (46) MDS-AML: CR: 44 (40) t-AML: CR: 49 (58) t-AML-MDS: CR: 4 (20) All $p > 0.05$	7 m 7 m $p > 0.05$	NA
Lee et al. (2017)	RCT, PROSP, Phase-III	Ara-C (200 mg/m^2 d: 1–7) + DNR (90 mg/m^2 d: 1–3) or Ara-C (200 mg/m^2 d: 1–7) + IDA (12 mg/m^2 d: 1–3)	17 7	49 (15–65) 49 (15–65)	CR: 2 (12) CR: 2 (29) $P = 0.32$	OS 4 y: 0 (0) OS 4 y: 0 (0) $p = 0.18$	EFS 4 y: 0 (0) EFS 4 y: 2 (33.3) $p = 0.083$

(continued)

Table 4.4 (continued)

Author (Year) [Reference]	Design	Treatment schedule	*N*	Age, median (range)	Induction outcome (*n* [%])	Median OS	Other survival outcomes
Lancet et al. (2018)	RCT, PROSP, Phase-III	Ara-C (100 mg/m^2 d: 1–7) + DNR (60 mg/m^2 d: 1–3) or CPX-351 (100 units/m^2 d: 1, 3, 5)	119 MDS-AML: 74 CMML-AML: 12 t-AML: 33 112 MDS-AML: 71 CMML-AML: 11 t-AML: 30	67.7 (60–75) 67.8 (60–75)	CR: 40 (34) MDS-AML, CR: 25 (34) CMML-AML, CR: 3 (25) t-AML, CR: 12 (36) CR: 50 (45) MDS-AML, CR: 32 (45) CMML-AML, CR: 4 (36) t-AML, CR: 14 (47)	6.0 m MDS-AML: 6.0 m CMML-AML: 2.3 m t-AML: 6 m NA MDS-AML: 7.4 m CMML-AML: 9.3 m t-AML: 12.2 m	NA

AHD-AML AML with an antecedent hematological disease, *AIDA* ATRA+IDA, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia, *Ara-C* cytarabine, *ATO* arsenic trioxide, *ATRA* all-trans-retinoic acid, *BSC* best supportive care, *CBF* core binding factor, *CHT* intensive chemotherapy, *CI* continuous infusion, *CMML-AML* AML with chronic myelomonocytic leukemia, *CR* complete remission, *CRi* complete response with incomplete blood recovery, *CRp* CR with incomplete platelet recovery, *CSA* ciclosporin, *d* days, *DNR* daunorubicin, *ECOG* Eastern Cooperative Oncology Group score, *ED* early death, *EFS* event-free survival, *ETOP* etoposide, *FLU* fludarabine, *HiDAC* high-dose cytarabine, *HSCT* hematopoietic stem cell transplantation, *IDA* idarubicin, *IQR* interquartile range, *LFS* leukemia-free survival, *m* months, *mDFS* median disease-free survival, *mEFS* median event-free survival, *MDS* myelodysplastic syndrome, *MDS-AML*: AML with MDS antecedent, *MPN* myeloproliferative neoplasm, *MIT* mitoxantrone, *mOS* median overall survival, *MPN-AML* AML with MPM antecedent, *N* population of the cohort, *NA* not available, *NRM* non-relapse mortality, *OS* overall survival, *PROSP* prospective study, *RCT* randomized clinical trial, *RES* resistance, *RETROSP* retrospective study, *RFS* relapse-free mortality, *RIC* reduced intensity conditioning, *RT* radiotherapy, *sAML* secondary AML, *sAPL* secondary APL, *t-AML* therapy-related AML, *t-AML-MDS* t-AML and MDS antecedent, *TRM* treatment-related mortality, *w* weeks, *y* year, *yo* years old, *2-CdA* cladribine

been a more accessible option for some older patients, mainly in those with favorable genetic risk (Zeidner et al. 2015; Stone et al. 2015; Löwenberg et al. 2009; Chauncey et al. 2010; Röllig et al. 2010; Müller-Tidow et al. 2016; Lancet et al. 2014). On the contrary, patients with poor PS, poor cytogenetics, high age (>75 years old), active malignant disease, or serious comorbidities should be considered for non-intensive approaches (e.g., HMAs, low-dose cytarabine [LDAC]) (Dumas et al. 2017).

Due to the poor prognosis, enrolment in clinical trials also remains the first option in this population (Fey and Buske 2013; Tallman et al. 2019). This strategy could allow some patients to benefit from innovative treatments and targeted therapies.

4.8.3 APL

Patients diagnosed with t-APL must receive therapeutic approaches comprising differentiating agents, such as anthracycline-based chemotherapy plus all-trans-retinoic acid (ATRA) or ATRA plus arsenic trioxide (ATO). Several studies have reported comparable results in t-APL as comparted to de novo APL in patients treated with ATRA plus chemotherapy regimens, while there is scarce information for t-APL patients treated with ATO-based regimens (Beaumont et al. 2003; Pulsoni et al. 2002; Elliott et al. 2012; Kayser et al. 2017; Dayyani et al. 2011). ATO plus ATRA regimens are now considered standard front-line for low- and intermediate-risk de novo APL, and are under investigation for high-risk patients (>10 × 10^9/L WBC counts). As t-APL patients are systematically excluded from clinical trials, clinical outcomes under chemotherapy-free approaches must be extrapolated from studies performed in de novo cases. Although upfront approaches with ATRA plus anthracycline can be suitable for t-APL, chemotherapy-free schedules are more appealing for t-APL patients to avoid additive toxicity of chemotherapy (Kayser et al. 2017; Dayyani et al. 2011). As suggested by some authors, the cumulative dose of chemotherapy may be related to higher rates of death during induction, higher incidence of toxic death, and development of t-MN after APL (Kayser et al. 2017).

4.8.4 New Approaches

Novel therapies have recently been approved for the treatment of AML. Although the majority of studies have focused on de novo AML patients, some of the following agents have been properly evaluated in sAML.

4.8.4.1 CPX-351

CPX-351 (Vyxeos®, Jazz Pharmaceuticals) is a liposomal formulation of cytarabine and daunorubicin at a 5:1 molar ratio, which is delivered into leukemic cells (Kim et al. 2011; Lim et al. 2010). CPX-351 liposomes could deliver daunorubicin and cytarabine in optimal ratio to maintain a synergistic effect. In addition, the liposomal formulation could lead to selective accumulation of both drugs in the bone marrow.

In a randomized phase 3 trial, CPX-351 showed longer OS and higher CR plus CR with incomplete recovery (CRi) rate in comparison with 7 + 3 schedule (median OS: 9.6 vs 5.6 months, $p = 0.005$; and CR + CRi: 47.7% vs 33.3%, $p = 0.016$, respectively) in fit patients aged between 60 and 75 years with untreated AML and the following characteristics: t-AML, MDS-AML with and without prior HMA, AML with a history of chronic myelomonocytic leukemia (CMML), and de novo AML with MDS-related cytogenetic abnormalities (Lancet et al. 2018).Toxicity was similar in both groups.

Currently, CPX-351 is the only therapy specifically approved for adults with newly diagnosed t-AML and MRC-AML by the US Food and Drug Administration (FDA) since 2017 and by the European Medicines Agency (EMA) since 2018 (Talati and Lancet 2018; Vyxeos n.d.).

4.8.4.2 Venetoclax

Venetoclax (Venclyxto/Venclexta®, AbbVie) is a small-molecule inhibitor of Bcl-2 that targets

AML cells whose survival could depend on anti-apoptotic proteins of the Bcl-2 family (Mihalyova et al. 2018).

Two studies contributed to the approval of venetoclax by the FDA in 2018, in combination with azacitidine or decitabine or LDAC, for the treatment of adult newly diagnosed AML patients aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (VENCLEXTA 2018). One of them was a phase 1/2 trial in which venetoclax plus LDAC was tested in 82 older patients with untreated AML, showing a CR + CRi rate of 35% in the group of patients with sAML (which represented 49% of the study cohort) (Wei et al. 2019). A phase 1b study explored venetoclax combined with HMA therapy (decitabine or azacitidine) in a similar cohort, but enrolled subjects could not have received HMAs for prior MDS or MDS/MPN. The CR + CRi rate in the subset of patients with sAML was 67% (DiNardo et al. 2019). Continued FDA approval for this indication is contingent upon verification of clinical benefit in confirmatory trials. Recently, the phase 3 trial VIALE-C comparing venetoclax plus LDAC versus placebo plus LDAC failed its primary endpoint of OS, although this was almost doubled in the experimental arm.

4.8.4.3 Gemtuzumab Ozogamicin (GO)

Gemtuzumab ozogamicin (GO; Mylotarg™, Pfizer) is a conjugate of an anti-CD33 antibody and the toxin calicheamicin. Its mechanism of action is based on the advantage of selective expression of CD33 by leukemic cells, but not in normal hematopoietic stem cells (Appelbaum and Bernstein 2017; Jen et al. 2018).

GO was approved by the FDA in 2017 and the EMA in 2018 for the treatment of adult patients with newly diagnosed CD33-positive AML, in combination with standard cytarabine and daunorubicin. Moreover, GO was also approved by the FDA as monotherapy for the treatment of patients ≥2 years of age with relapsed/refractory CD33-positive AML.

Although recent clinical trials have evaluated the possibility of adding GO to traditional schedules for the treatment of sAML patients, their results have not supported further development in this setting (de Witte et al. 2015; Burnett et al. 2011).

4.8.4.4 Glasdegib

The hedgehog signaling pathway is an attractive novel therapeutic target because of its biologic role in the maintenance and expansion of leukemic stem cells and 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 function in the canonical hedgehog pathway (DAURISMO 2018).

In a randomized phase 2 study performed in unfit patients with newly diagnosed AML or high-risk MDS, glasdegib in combination with LDAC showed longer OS and achieved a higher CR rate than LDAC alone (Cortes et al. 2019). Afterward, glasdegib plus LDAC was approved by the FDA in 2018 for the treatment of newly diagnosed adult AML patients aged ≥75 years or who have comorbidities that preclude use of intensive induction chemotherapy (DAURISMO 2018). However, analysis of sAML patient group included in this study has not yet been published.

4.8.4.5 *IDH* Inhibitors

Leukemic IDH1 and IDH2 mutations confer a neomorphic enzymatic activity, impairing hematopoietic differentiation and promoting leukemogenesis (Figueroa et al. 2010). Mutations in IDH1 occur in approximately 6–10% of patients with AML and IDH2 mutations occur in 9–13% (DiNardo et al. 2018). Similar incidence has been reported in sAML (Ok et al. 2015a).

Ivosidenib (Tibsovo®, Agios) and enasidenib (Idhifa®, Celgene) induce myeloid differentiation and reduce blast counts by inhibiting mutant IDH1 and mutant IDH2, respectively (IDHIFA 2017; TIBSOVO 2018). The approval of ivosidenib by the FDA in 2018 was based on results of a phase 1 study, performed in adult patients with relapsed/refractory IDH1-mutated AML (35% were sAML). With ivosidenib monotherapy, a CR + CRi rate of 30% was achieved

(DiNardo et al. 2018). Enasidenib was approved by the FDA in 2017 for the treatment of adult patients with relapsed or refractory IDH2-mutated AML. The results of a phase 1/2 trial with a CR + CRi rate of 26% and median OS of 9.3 months led to its approval (Stein et al. 2017).

4.8.4.6 *FLT3* Inhibitors

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane receptor tyrosine kinase specially expressed on hematopoietic progenitor cells and is involved in differentiation and proliferation (Lyman and Jacobsen 1998; McKenna et al. 2000). *FLT3-ITD* mutation occurs less frequently in patients with sAML than in de novo (9% vs 26%, respectively) and predicts a poor prognosis (Fröhling et al. 2002; Stone et al. 2018). Midostaurin (Rydapt®, Novartis), a small-molecule inhibitor of FLT3, was approved by the FDA and EMA in 2017 for the treatment of adult patients with newly diagnosed FLT3-mutated AML, in combination with cytarabine and daunorubicin chemotherapy (Stone et al. 2018). In a randomized phase 3 RATIFY study, midostaurin plus conventional chemotherapy showed longer OS and EFS compared with chemotherapy alone in *FLT3* mutated patients aged ≤60 years with newly diagnosed AML (Stone et al. 2017). Of note, sAML patients were excluded from the RATIFY trial. Gilteritinib (Xospata®, Astellas Pharma) is other FLT3 kinase inhibitor, recently approved by FDA in 2018 for the treatment of adult patients with relapsed/refractory AML (XOSPATA 2018). Unfortunately, t-AML patients were excluded in all phase 3 trials with FLT3 inhibitors, and no data for second-generation inhibitors (gilteritinib or quizartinib) have yet been published with regard to MDS-AML.

4.9 Future Directions

Currently, patients diagnosed with sAML have a dismal prognosis, either because of the adverse biological features of the disease or the patient's clinical characteristics. Scientific groups are continuously updating their treatment protocols to design tailored therapies according to prognostic factors, including sAML as a relevant decision factor. Nevertheless, there is an increasing need to improve treatment strategies for sAML patients, which may represent one of the most challenging AML subsets. In particular, older patients with sAML may represent a very frequent subgroup where no specific approaches have been designed. There is room for advances in this challenging population, but these will be obtained only through well-designed specific protocols. In this regard, the clinical development of CPX-351, from phase 2 to phase 3, is a good example of success within this therapeutic area.

The better understanding of molecular mechanisms of leukemogenesis has led to the development of new targeted molecules focusing on actionable mutations and pathways. Unfortunately, patients with sAML are often excluded from clinical trials and only some new agents have been tested in this subset of patients with promising results. CPX-351 was approved for adults with newly diagnosed t-AML or MRC-AML, venetoclax in combination with LDAC or HMAs has remarkable activity in unfit subjects, glasdegib was shown to be able to benefit unfit sAML patients, and *IDH1/IDH2* inhibitors may be an option at least for relapsed/refractory sAML.

Based on new scientific evidence, the treatment landscape in sAML may change toward: (1) replacement of conventional 7 + 3 chemotherapy by CPX-351 as a backbone for fit patients; (2) combination of CPX-351 with a *FLT3* or *IDH* inhibitor in sAML fit patients with *FLT3* or *IDH* mutations; and (3) combination of venetoclax with HMAs or LDAC for patients considered unfit to receive intensive chemotherapy. The role of targeted- vs venetoclax- vs triple combinations-based approaches for unfit sAML harboring actionable mutations must be elucidated in the future.

We should highlight two groups of sAML patients in whom therapeutic improvements have not been achieved yet. The first group constitutes MRC-AML following HMA therapy. These patients are systematically excluded from phase 3 clinical trials in which an HMA is the control

arm, so no evidence-based advances will be available for these patients from the majority of ongoing phase 3 trials. Only the combinations of glasdegib plus LDAC or venetoclax plus LDAC regimens could be applied in these patients with some background evidence, but unfortunately those regimens do not represent a therapeutic breakthrough for this population. On the other hand, younger fit patients developing sAML after HMA therapy have been classically treated with 3 + 7 or similar regimens and more recently with CPX-351, showing poor clinical outcomes in both scenarios. The second group of very difficult-to-treat sAML is composed by MRC-AML evolving from MPN. These patients are usually excluded from clinical trials, including the recently sAML-focused CPX-351 phase 3 trial.

Additionally, some early development stage therapies for AML may become promising treatment approaches for sAML patients. Some examples are chimeric antigen receptor T cells or agents targeting the *TP53* pathway, which should be evaluated in patients with sAML in forthcoming studies.

4.10 Conclusions

According to the 2016 WHO classification, sAML is included in two diagnostic groups: t-MN, along with therapy-related MDS/MPN; and MRC-AML, along with non-secondary AML subtypes (Arber et al. 2016; Döhner et al. 2017). The incidence of sAML is estimated between 20 and 30% of all AML (Juliusson et al. 2009; Bertoli et al. 2017; Medeiros et al. 2015; Hulegårdh et al. 2015; Østgård et al. 2010, 2015; Gangatharan et al. 2013; Szotkowski et al. 2010), with most of them having a prior history of MDS or MPN (Hulegårdh et al. 2015; Østgård et al. 2010). Although sAML has commonly been considered an independent adverse prognostic condition, this might be questionable as sAML is closely related to older age, comorbidities, worse PS, and unfavorable genetic features (Larson 2007; Stölzel et al. 2011; Pulsoni and Pagano 2005; Rizzieri et al. 2009). These baseline characteristics also lead physicians to frequently consider sAML patients unfit to receive curative therapies or be included in clinical trials.

The frequency of adverse features, such as older age, worse PS, and adverse karyotype and molecular profile, is by far higher in sAML than in de novo AML. However, the most relevant prognostic factor in AML is the therapeutic approach itself, which is probably intended as curative option in the minority sAML patients. Enrolling sAML patients in clinical trials should be a priority, and whenever possible, they should be referred to an appropriate research center where experimental options are available. Only patients with hopeless prognosis who do not meet criteria to participate in these studies should be approached in a palliative way. Given the challenging condition that they represent, obtaining improvements in sAML should be a priority, warranting that this field is becoming an active area of basic and clinical research in the forthcoming years.

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