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Characterization and prognostic factors of secondary to MDS/MPN and therapy-related AML: a single-center study

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Abstract

Introduction: Secondary acute myeloid leukemia (sAML) accounts for 15–30% of overall AML cases and is associated with shorter survival compared to de novo AML. The pathogenetic spectrum of sAML is heterogeneous, i.e. therapy-related AML (tAML) arises from prior cytotoxic, radiation, or immunosuppressive therapy, while myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN)-AML develops from a previous clonal disorder of hematopoiesis.

Material and methods: We performed a single-center retrospective analysis of MDS/MPN-AML and tAML patients diagnosed between 2013 and 2018 in the Hematology Department of the Medical University in Lodz, Poland. Simultaneously, demographic data, clinical factors, and laboratory findings were collected. For statistical analysis, we used Cox proportional hazard models and log-rank tests.

Results: The study included 110 patients with either MDS/MPN-AML (n = 78) or tAML (n = 32), with a median age of 66 years (range 31–86). The median follow-up was 3.2 months [95% confidence interval (CI): 2.5–5.3]. The median overall survival (OS) for MDS/MPN-AML patients was 4.1 months (95% CI: 2.5–7.0) and for tAML it was 2.8 months (95% CI: 1.6–5.6). In multivariate Cox regression model for OS, factors such as age at diagnosis [hazard ratio (HR) 1.03, 95% CI: 1.00–1.06), higher Eastern Cooperative Oncology Group score (HR 1.85, 95% CI: 1.08–3.15), hypoalbuminemia (HR 3.20, 95% CI: 1.95–5.24) and percentage of bone marrow blasts infiltration (HR 1.01, 95% CI: 1.00–1.03) were independent predictors of poor survival for the whole cohort. On the other hand, the intensive treatment approach was related to longer survival (HR 0.42, 95% CI: 0.21–0.82). There were no differences in OS between MDS/MPN-AML and tAML (p = 0.81).

Conclusion: The poor treatment outcomes for sAML consist of a combination of low response rate and high early mortality. The positive influence of intensive chemotherapy should be highlighted, but nevertheless, optimizing treatment for this high-risk subpopulation remains crucial.

Key words: acute myeloid leukemia, secondary AML, treatment-related AML, MDS/MPN AML, overall survival

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Introduction

Secondary acute myeloid leukemia (sAML) is a term given to AML developing out of preceding myeloid malignancies i.e. myelodysplastic syndromes or myeloproliferative neoplasm (MDS/MPN-AML). However, in the literature this term also includes AML arising after prior exposure to cytotoxic therapy and/or radiotherapy for malignant or

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non-malignant disease, which corresponds to the World Health Organization (WHO) 2016 definition of therapy-related AML (tAML) [1]. Classically, tAML is divided according to the causative agent into type 1, which is associated with prior treatment with alkylating agents or ionizing radiation, and type 2, which follows treatment with topoisomerase II inhibitors [2, 3].

Type 1 tAML usually appears 4–7 years after treatment, and approximately two-thirds of patients have a preceding MDS. High frequency of abnormalities involving the long arm of chromosome 5 [del(5q)], the long arm of chromosome 7 [del(7q)], or loss of chromosome 7 (del7) is also characteristic of this type.

In type 2 tAML, the latency period is shorter, and the disease usually develops 2–3 years after treatment, without a preceding myelodysplastic phase and with common balanced chromosomal translocations involving 11q23 (*MLL*) or 21q22 (*RUNX1*) [2, 4]. The most frequently mutated genes in sAML are those related to DNA methylation (46%), chromatin modification (42%), RAS signaling (42%), RNA spliceosome machinery (55%), transcriptional regulation (34%), and those related to proteins that regulate the three-dimensional organization of chromatin in the nucleus (22%) [5]. Analyzing the molecular findings for MDS/MPN-AML, the presence of mutations in the *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR* or *STAG2* genes is highly specific [6].

Although the latest classification for AML, according to European LeukemiaNet (ELN) in 2022, removed sAML from the main classification categories, the features of that subtype are still clinically important and have been applied as diagnostic qualifiers to the AML-defining category [7]. Similarly, the International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias 2022 emphasizes the role of prior therapy as well as antecedent myeloid neoplasms in the development of AML and also distinguishes them as diagnostic qualifiers [8]. The reason for exclusion as an independent entity is the current emphasis on categorizing AML based on genetic alterations. Simultaneously, in 2022 the WHO's Classification of Hematolymphoid Tumors was published. However, this maintained the AML myelodysplasia related (AML-MR) categorization, although changing the name to AML "with myelodysplasia-related changes" (AML-MRC) and updating the diagnostic criteria. The key changes are the removal of morphology as the sole factor determining the diagnosis of AML-MR, the updating of the cytogenetic criteria, and the introduction of mutations of eight genes that mandate the diagnosis i.e. *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR,* and *STAG2*. MDS/MPN-AML continues to be defined under AML-MR in view of the broader unifying biological features, while tAML categorization, referred to myeloid neoplasms post cytotoxic therapy (MN-pCT), also remains classified after slight modifications [9].

sAML is characterised by a poor prognosis with an estimated survival of 6–12 months and it is considered to be a risk factor for early death in some prognostic models compared to *de novo* AML [2]. However, it is still a challenge to describe in detail the mechanisms and reasons for unsatisfactory treatment outcomes. There have been many population-based analyses characterizing possibly crucial factors. Nevertheless, the independent prognostic value of sAML itself has been questioned, as the diagnosis is often associated with older age, frequent comorbidities/organ dysfunction, and an unfavorable cytogenetic and molecular profile [10].

In this study, we aimed to characterize MDS/MPN-AML and tAML patients treated at our center and to evaluate relevant prognostic factors in these subtypes of AML.

Material and methods

We conducted a comprehensive analysis of adult patients diagnosed with AML in the Department of Hematology at the Medical University in Lodz, Poland, between 2013 and 2018. We developed a database of AML patients to search for significant prognostic features and to compare and characterize particular subtypes of sAML in our region. We based our study on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) classification and searched for data via the medical records. Patients were assigned to either an MDS/MPN-AML group or a tAML group, according to the WHO 2016 classification [1] (MDS/MPN-AML and tAML were defined as previously described).

The cytogenetic risk profile was classified as favorable, or intermediate, or adverse according to the ELN 2017 criteria [11]. Patients eligible for intensive chemotherapy were treated according to Polish Acute Leukemia Group (PALG) protocols, while the unfit or elderly population was given low-intensity treatment or best supportive care. The intensive treatment included induction chemotherapy based on daunorubicin (DNR 60 mg/m^2 i.v., days 1–3) and cytarabine (Ara-C, 200 mg/m^2 i.v., days 1–7) — DA or DA with cladribine (5 mg/m^2 i.v., days 1–5) (DAC) or for patients aged over 60 — DA/DAC with reduced dose of Ara-C (100 mg/m^2 i.v., days 1–7). The post-remission therapy was based on high/intermediate-dose cytarabine regimens with a subsequent allogeneic hematopoietic stem cell transplantation (allo-HSCT). The non-intensive treatment included repeated courses of azacitidine (AZA) 75 mg/m^2, days 1–7, low-dose of Ara-C (LD-Ara-C) 20 mg/m^2, days 1–10, cytoreduction with hydroxyurea or 6-mercaptopurine, or best supportive care (BSC) alone. The functional status of patients was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale. The patients' characteristics are set out in Table I.

Table I. Patients' characteristics

Variable	MDS/MPN-AML	tAML
Patients, n	78	32
Gender, n [%]:		
• female	32 (41)	19 (59)
• male	46 (59)	13 (41)
Age at diagnosis, median (IQR)	66 (60–71.75)	67.5 (62.75–72)
Age distribution, n [%]:		
• <60 years	19 (24)	5 (16)
• ≥60 years	59 (76)	27 (84)
Primary disease, n [%]	MDS 48 (62) MPN 30 (38)	Breast 9 (28) Prostate 6 (19) Other 17 (53)
ECOG, n [%]:		
• 0	36 (46)	11 (34)
• 1	25 (32)	9 (28)
• 2	11 (14)	10 (31)
• 3	2 (3)	2 (6)
• 4	3 (4)	0
• no data	1 (1)	
Cytogenetic risk profile, n [%]:		
• 1	2 (3)	2 (6)
• 2	28 (36)	5 (15)
• 3	16 (21)	13 (41)
• no data	32 (41)	12 (37)
WBC at dgn. [G/L], median (IQR)	6 (1.9–42)	6.21 (1.98–66.66)
ANC at dgn. [G/L], median (IQR)	1.25 (0.5–11.2)	1.22 (0.27–9.91)
PB blasts at dgn. [%], median (IQR)	14 (4–45)	2.5 (0–30)
PLT at dgn. [G/L], median (IQR)	45.5 (21.2–107)	45 (21.5–80)
Hb at dgn. [g/dL], median (IQR)	8.3 (7.4–9.2)	8.4 (6.9–9.6)
LDH at dgn. [U/L], median (IQR)	282 (230–559)	350.5 (222.7–506)
Uric acid [mg/dL], median (IQR)	6.1 (4.6–8.2)	5.5 (4.7–7.2)
Albumin [g/dL], mean ± SD	3.6 ± 0.67	3.8 ± 0.61
BM blasts at dgn. [%], median (IQR)	35 (25–55)	45 (27.5–63.2)
Dysplasia (lines), n [%]:		
• 1	9 (11.5)	7 (22)
• 2	24 (31)	14 (44)
• 3	39 (50)	9 (28)
• no data	6 (7.5)	2 (6)
Intensive treatment, n [%]:		
• all age groups	22 (28)	5 (15.5)
• <60 years	16 (84)	3 (60)
• ≥60 years	6 (10)	2 (7)
Non-intensive treatment, n [%]:		
• LD-Ara-C	22 (28)	15 (47)
• AZA	16 (21)	4 (12.5)
• cytoreduction or BSC	18 (23)	8 (25)
Response rates, n [%]:		
• CR	13 (17)	5 (15.5)
• PR	18 (23)	7 (22)
• NR	8 (10)	5 (15.5)
• PD	20 (26)	12 (38)
• ED	19 (24)	3 (9)

→

Table I (cont.). Patients' characteristics

Variable	MDS/MPN-AML	tAML
Time since primary disease dgn. to AML dgn., median (IQR) [months]	13.5 (4.3–30)	90 (38.5–112.0)
OS since primary disease dgn., median (IQR) [months]	26 (11–48.7)	94 (44.0–119.0)
OS since AML dgn., median (IQR) [months]	4.1 (1.1–13.7)	2.8 (1.4–8.2)

MDS/MPN-AML — acute myeloid leukemia secondary to myelodysplastic syndrome/myeloproliferative neoplasm; tAML — therapy-related AML; n — number; IQR — interquartile range; ECOG — Eastern Cooperative Oncology Group scale; WBC — white blood count; dgn. — diagnosis; ANC — absolute neutrophil count; PB — peripheral blood; PLT — platelets; Hb — hemoglobin; LDH — lactate dehydrogenase; SD — standard deviation; BM — bone marrow; LD-Ara-C — low-dose of cytarabine; AZA — azacytidine; BSC — best supportive therapy; CR — complete remission; PR — partial remission; NR — no response; PD — progressive disease; ED — early death; AML — acute myeloid leukemia; OS — overall survival

Table II. Univariate analysis of overall survival in both therapy-related acute myeloid leukemia and acute myeloid leukemia secondary to myelodysplastic syndrome/myeloproliferative neoplasm patients

Variable	Coefficient	*p*	HR	95% CI	
				Lower	Upper
Age at dgn.	0.04	0.00	1.04	1.02	1.06
Age at dgn. ≥60 years	0.78	0.00	2.18	1.28	3.69
ECOG 0/1 vs. 2/3/4	0.90	0.00	2.47	1.56	3.92
Cytogenetic risk low/intermediate vs. high according to ELN 2017	1.02	0.00	2.76	1.61	4.73
WBC at dgn.	0.00	0.27	1.00	1.00	1.01
WBC at dgn. >20 G/L	0.21	0.33	1.23	0.81	1.87
WBC at dgn. >50 G/L	0.12	0.63	1.12	0.70	1.80
ANC at dgn.	0.01	0.14	1.01	1.00	1.01
PB blasts at dgn.	0.01	0.01	1.01	1.00	1.02
PLT at dgn.	0.00	0.48	1.00	1.00	1.00
Hb at dgn.	–0.09	0.07	0.91	0.83	1.01
LDH at dgn.	0.00	0.01	1.00	1.00	1.00
LDH norm vs. above norm	0.06	0.81	1.06	0.66	1.71
Uric acid at dgn.	0.06	0.14	1.06	0.98	1.15
Uric acid norm vs. above norm	0.35	0.10	1.41	0.94	2.13
Albumins at dgn.	–0.38	0.04	0.68	0.47	0.99
Albumins norm vs. below norm	0.54	0.02	1.72	1.08	2.74
BM blasts at dgn.	0.02	0.00	1.02	1.01	1.03
BM blasts ≥50%	0.64	0.00	1.90	1.26	2.88
BM blasts ≥60%	0.69	0.01	2.00	1.23	3.25
Dysplasia in 1 vs. 2/3 lines	0.33	0.25	1.40	0.79	2.47
Intensive vs. non-intensive treatment	–1.11	0.00	0.33	0.20	0.55
Time from primary disease dgn. to AML dgn.	0.00	0.05	1.00	1.00	1.01

HR — hazard ratio; CI — confidence interval; dgn. — diagnosis; ECOG – Eastern Cooperative Oncology Group scale; ELN — European LeukemiaNet; WBC — white blood count; ANC — absolute neutrophil count; PB — peripheral blood; PLT — platelets; Hb — hemoglobin; LDH — lactate dehydrogenase BM — bone marrow; AML — acute myeloid leukemia

Statistical analysis

We performed a survival analysis and created a Cox proportional hazards model. We calculated the median overall survival (OS) for the MDS/MPN-AML and tAML groups, as well as the median OS from diagnosis of primary cancer. We performed a comparison of survival in groups divided according to the selected variables using the log-rank test. Initially we created a univariate analysis of OS for all patients (Table II) and selected the variables with the highest level of statistical significance. Next, we created a Cox proportional hazards regression model including covariates with $p < 0.15$. As a result, this included quantitative variables such as albumin level, percentage of blasts in the bone marrow (BM) and age, and qualitative variables such as cytogenetic risk, ECOG grade, and type of treatment. We considered variables with $p < 0.05$ as

Table III. Cox proportional-hazard regression for overall survival in both therapy-related acute myeloid leukemia and acute myeloid leukemia secondary to myelodysplastic syndrome/myeloproliferative neoplasm patients

Variable	Coefficient	*p*	HR	95% CI	
				Lower	Upper
Albumin (norm vs. below norm)	1.16	<0.00	3.20	1.95	5.24
Blasts BM [%]	0.01	0.02	1.01	1.00	1.03
Cytogenetic risk (low/intermediate vs. high)	0.39	0.11	1.48	0.92	2.38
ECOG (0/1 vs. 2/3/4)	0.62	0.02	1.85	1.08	3.16
Intensive vs. non-intensive treatment	–0.87	0.01	0.42	0.21	0.81
Age at AML diagnosis	0.03	0.04	1.03	1.00	1.06

HR — hazard ratio; CI — confidence interval; BM — bone marrow; ECOG — Eastern Cooperative Oncology Group scale; AML — acute myeloid leukemia

significant independent prognostic factors (Table III). Confidence intervals for the hazard ratio were set at 95%. The software used was Statistica 13.1 (TIBCO Software Inc.) and MedCalc Software Ltd.

Results

A total of 110 patients from the database [78 with MDS/MPN-AML and 32 with tAML; women 46% (n = 51); men 54% (n = 59)] was included. The median age at diagnosis was 66 years [interquartile range (IQR) 60–71.75] for MDS/MPN-AML and 67.5 years (IQR 62.75–72) for tAML (p = = 0.51). In the MDS/MPN-AML group, 76% (n = 59) of patients were aged 60 years or above, while in the tAML group, they accounted for 84% (n = 27). The baseline clinical and laboratory parameters are detailed in Table I. Among MDS/MPN-AML patients, myelodysplastic syndrome was the most common antecedent disorder (n = 48; 62%), and myeloproliferative diseases accounted for 38% (n = 30). Regarding patients with tAML, the most common primary solid tumors were breast cancer (n = 9; 28%) and prostate cancer (n = 6; 19%) (Table IV).

As for laboratory parameters, there were no differences in peripheral blood morphology values, nor in biochemical exponents, between the groups (p >0.05). The median percentage of blasts in peripheral blood was 14% for MDS/MPN-AML and 2.5% for tAML (p = 0.007), while the percentage of blasts in BM was 35% vs. 45%, respectively (p = 0.22).

Overall, the proportion of patients referred to intensive chemotherapy was only 25%. In the MDS/MPN-AML group, intensive treatment was administered to 28% of patients (n = 22), of whom 16 were <60 and six patients were ≥60. For the tAML group, only 16% of patients (n = 5) were intensively treated, comprising three patients <60 and two ≥60. Considering patients treated non-intensively, LD-Ara-C therapy was given to 33.5% of patients (n = 37), AZA to 18% (n = 20), and 23.5% of patients were qualified for cytoreduction or BSC alone (n = 27). The division into MDS/MPN and tAML groups is included in Table I.

Allo-HSCT was performed in nine patients, of whom five received myeloablative (MAC) and four reduced-intensity (RIC) conditioning. One patient underwent two allo-HSCTs with an interval of two years. The mean age in this group was 47 years [standard deviation (SD) ± 11.6], and two patients were >60. Median OS for patients undergoing allo-HSCT was 18.8 months (95% CI: 4.4–35.6 months).

Complete remission (CR) was achieved in 16% (n = = 18) of patients, 23% (n = 25) had partial remission (PR), 12% (n = 13) had no response to the applied treatment (NR), 29% (n = 32) of patients experienced disease progression despite therapy, and 20% (n = 22) suffered early death (ED), defined as death within 28 days from the start of treatment. Considering intensively treated patients, CR was achieved by 56% (n = 15) and PR by 22% (n = 6) (78% CR + PR, n = 21). Among patients not treated intensively, 4% achieved CR (n = 3; two patients treated with AZA and one treated with LD-Ara-C), and 23% achieved PR (n = 19). The division into MDS/MPN and tAML groups considering each response rate is included in Table I.

The median time from primary disease diagnosis to AML was 13.5 months (IQR 4.2–30) for MDS/MPN-AML, and 90 months (IQR 38.5–112.0) for tAML. The median OS from primary disorder diagnosis was 26 months (IQR 11–48.7, 95% CI: 21–32) and 94 months (IQR 42.0–119.0, 95% CI: 66–114) for MDS/MPN-AML and tAML, respectively. Survival in the whole sAML group was very poor, with median OS of 3.1 months (IQR 1.4–13, 95% CI: 2.5–5.3) consisting of 4.1 months (IQR 1.1–13.7, 95% CI: 2.5–7.0) for MDS/MPN-AML and 2.8 months (IQR 1.4–8.2, 95% CI: 1.6–5.6) for tAML patients; no statistical difference was observed between the groups (p = 0.81) (Figure 1).

Median OS for the entire cohort was significantly longer for patients with low (median not reached) versus intermediate (13.2 months) versus high (2.8 months) cytogenetic risk, respectively, (p = 0.0001) (Figure 2A). Moreover, patients with an initial BM blast level below 50% had longer survival (5.5 vs. 1.6 months) (p = 0.001) (Figure 2B). A comparison of survival in patients treated with intensive versus non-intensive therapeutic approaches

Table IV. Distribution of primary disorders/cancers among patients with secondary acute myeloid leukemia

Variable	Primary disorder/cancer	Number of cases	Percentage of MDS/MPN-AML/tAML	Percentage of all cases
MDS/MPN-AML	MDS	48	61.5%	43.6%
	PV	7	9.0%	6.4%
	PMF	7	9.0%	6.4%
	CMML	7	9.0%	6.4%
	CML	5	6.4%	4.5%
	ET	3	3.8%	2.7%
	CNL	1	1.3%	0.9%
tAML	Breast	9	28.1%	8.2%
	Prostate	6	18.8%	5.5%
	Colon	5	15.6%	4.5%
	Ovaries	3	9.4%	2.7%
	Hodgkin lymphoma	3	9.4%	2.7%
	Stomach	1	3.1%	0.9%
	Endometrium	1	3.1%	0.9%
	DLBCL	1	3.1%	0.9%
	Lung	1	3.1%	0.9%
	Thyroid	1	3.1%	0.9%
	Sarcoma	1	3.1%	0.9%

MDS/MPN-AML — acute myeloid leukemia secondary to myelodysplastic syndrome/myeloproliferative neoplasm patients; tAML — therapy-related acute myeloid leukemia; MDS — myelodysplastic syndrome; PV — polycythemia vera; PMF — primary myelofibrosis; CMML — chronic myelomonocytic leukemia; CML — chronic myeloid leukemia; ET — essential thrombocytopenia; CNL — chronic neutrophilic leukemia; DLBCL — diffuse large B-cell lymphoma

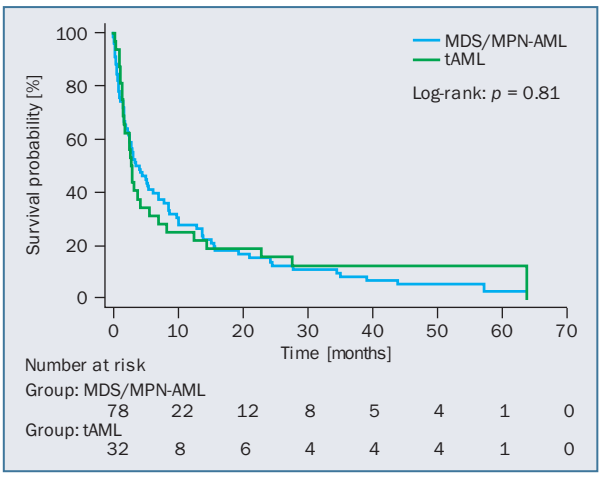

Figure 1. Kaplan-Meier curves for overall survival in secondary acute myeloid leukemia patients, acute myeloid leukemia secondary to myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN-AML) versus therapy-related acute myeloid leukemia (tAML) patients

showed a significant advantage in OS for the intensively treated group (13.9 vs. 2.5 months, p <0.0001) (Figure 3A). Moreover, OS analysis showed longer survival in patients <60 vs. ≥60 (7.9 vs. 2.8 months, p = 0.002) (Figure 3B). Comparing OS among patients with overall performance status classified as 0 or 1 in the ECOG scale versus 2–4 showed significantly longer survival in the former group than the latter (4.3 vs. 1.2 months, p = 0.001). Taking each ECOG grade separately, a trend toward longer survival was proven for patients with lower grades, with the longest survival being for grade 0 (7.0 months) and the shortest for grade 4 (0.2 months) (Figure 4A). Comparative OS analysis for the albumin level showed shorter survival in patients with hypoalbuminemia (defined by albumins concentration <3.5 g/dL) (6.2 vs. 2.5 months, p = = 0.012) (Figure 4B). The median follow-up was 3.2 months (95% CI: 2.5–5.3).

Regarding the univariate Cox proportional hazards model for OS, significant factors with potential prognostic importance for shorter survival were: age ≥60 years [hazard ratio (HR) 2.18, 95% CI: 1.28–3.69], ECOG >1 (HR 2.47, 95% CI: 1.56–3.92), high-risk cytogenetics (HR 2.76, 95% CI: 1.61–4.73), higher percentage of blasts in peripheral blood (HR 1.01, 95% CI: 1.00–1.02), higher LDH (HR 1.00, 95% CI: 1.00–1.00), hypoalbuminemia (HR 1.72, 95% CI: 1.08–2.74), higher BM infiltration (HR 1.02, 95% CI: 1.01–1.03), blasts in BM >50% (HR 1.90, 95% CI: 1.26–2.88) and >60% (HR 2.00, 95% CI: 1.23–3.25), and longer time to sAML diagnosis calculated from the primary disease diagnosis (HR 1.00, 95% CI: 1.00–1.01).

It is worth emphasizing that variables such as albumin level (HR 0.68, 95% CI: 0.47–0.99) and intensive therapeutic approach (HR 0.33, 95% CI: 0.20–0.55) were important

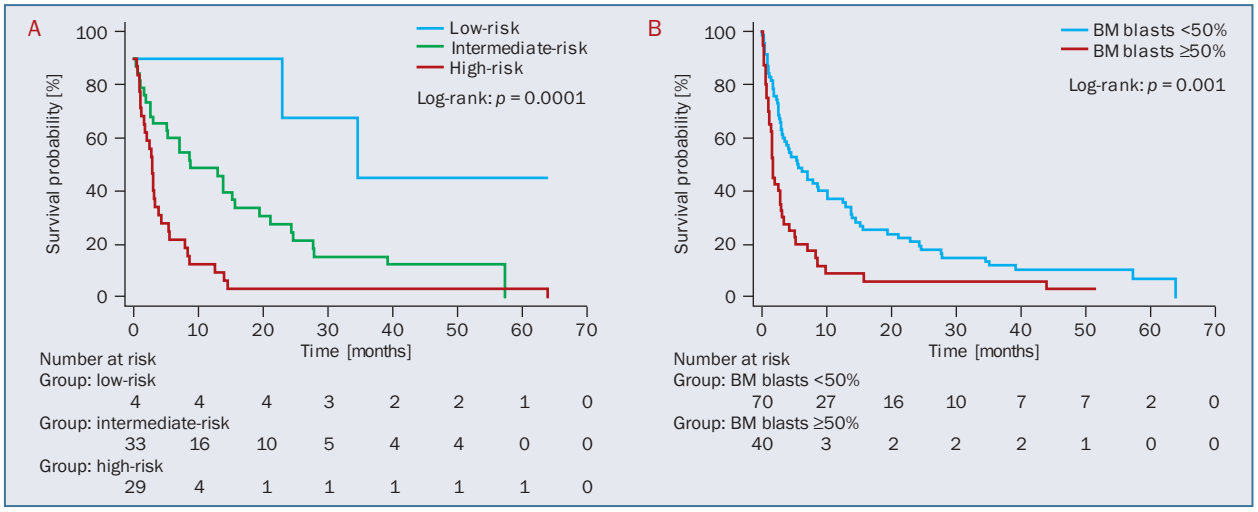

Figure 2. Kaplan-Meier curves for overall survival in secondary acute myeloid leukemia patients: **A.** Comparing cytogenetics risk, low versus intermediate versus high; **B.** Comparing bone marrow (BM) blasts infiltration, <50% versus ≥50%

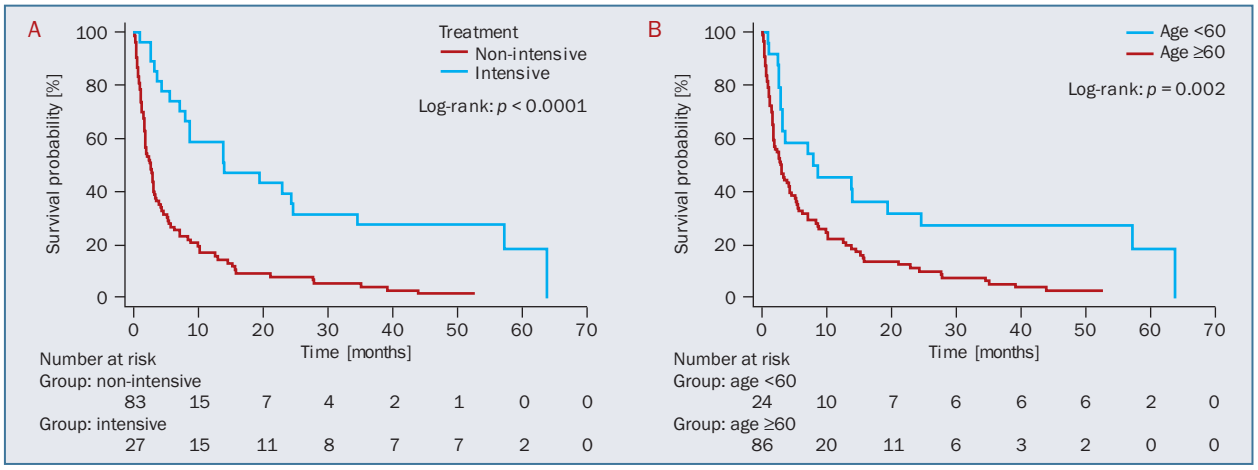

Figure 3. Kaplan-Meier curves for overall survival in secondary acute myeloid leukemia patients: **A.** Comparing patients treated intensively versus non-intensively; **B.** Depending on age at diagnosis, <60 versus ≥60 years

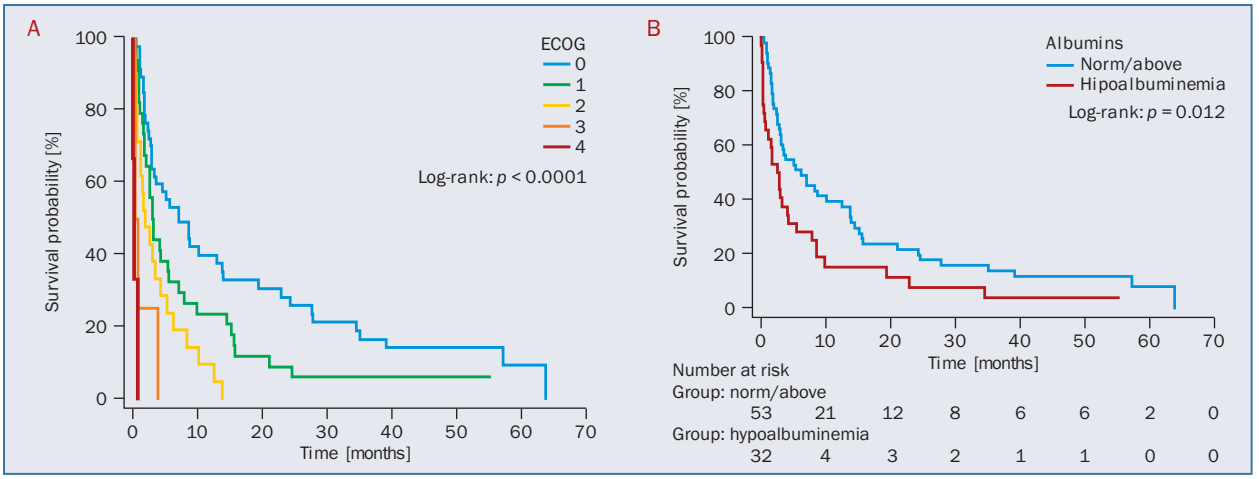

Figure 4. Kaplan-Meier curves for overall survival in secondary acute myeloid leukemia patients: **A.** Comparing patients stratified by Eastern Cooperative Oncology Group (ECOG) score; **B.** Comparing patients with and without hypoalbuminemia

for improving prognosis. The analysis in detail, including other studied factors, is presented in Table II.

Multivariate Cox proportional hazards model showed age at AML diagnosis (HR 1.03, 95% CI: 1.00–1.06), ECOG >1 (HR 1.85, 95% CI: 1.08–3.16), percentage of BM infiltration by blasts (HR 1.01, 95% CI: 1.00–1.03), and hypoalbuminemia (HR 3.20, 95% CI: 1.95–5.24) as independent prognostic factors for worsening OS. On the other hand, an intensive therapeutic approach was found to be an independent prognostic factor acting favorably for OS (HR 0.42, 95% CI: 0.21–0.81). High cytogenetic risk seemed to negatively affect survival (HR 1.48, 95% CI: 0.92–2.38), but remained without statistical significance ($p = 0.11$). Details of the multivariate Cox proportional hazards model for OS are set out in Table III.

Discussion

The incidence of sAML appears to have increased in recent years, due to the more widespread use of radio-chemotherapy and the greater long-term survival of cancer patients. sAML accounts for 15–30% of AML cases, with 18–20% being MDS/MPN-AML and 6–8% tAML [2, 12, 13]. In the PETHEMA registry study, 2,310 patients with sAML were analyzed. Of them, MDS-AML accounted for 44%, tAML for 25%, MPN-AML for 11%, MDS/MPN-AML for 10%, and antecedent neoplasia without prior chemo/radiotherapy (neo-AML) for 9% [13]. In our analysis, MDS-AML accounted for 44% of sAML cases, MPN-AML for 27%, and tAML for 29%. Our frequency of recognizing particular types of sAML was also similar to data that has been reported by other centers [14, 15].

sAML is associated with a lower rate of complete responses; according to our results, only 16% of patients achieved CR and 23% PR, with the majority receiving non-intensive treatment. Among the intensively treated, the percentages were 56% and 22%, respectively. These results were similar to those obtained by Schuler et al. [16], in patients with high-risk MDS and MDS-AML, where CR after the first induction was 50% and PR 22%.

The prognosis in sAML remains poor, with frequent resistance to conventional chemotherapy and OS shorter than 12 months [17]. Considering tAML and MDS/MPN-AML together often blurs the clinical and prognostic differences between them. In our study, OS for all sAML patients was 3.1 months, with the worst result being for the group of patients with tAML, at 2.8 months, whereas for MDS/MPN-AML it was 4.1 months. These results are relatively consistent with the observations of the PETHEMA registry, in which the median OS for sAML was 5.6 months. In analysis performed on 95 sAML patients by Koh et al. [15], median OS for MPN-AML, MDS-AML, and tAML was 3.9, 6.6, and 8.7 months, respectively. Meanwhile, Lalayanni et al. [18] analyzed 149 patients with sAML and found no difference in median overall survival (mOS) between MDS/MPN-AML and tAML patients. The shorter survival in our study compared to those mentioned above may be due to the more advanced age and more comorbidities, and as a result the lower percentage of patients who were eligible for intensive treatment, with few patients receiving allo-HSCT.

The 2-year survival of sAML patients after allo-HSCT ranges from 20–30% [19, 20] and is shorter than in the entire AML population of patients undergoing this procedure (as salvage therapy in AML, the procedure achieves a 3-year OS of 44%, while in CR2 59%) [21]. However, Lalayanni et al. [18] showed that allo-HSCT recipients in CR1 had superior median OS compared to patients without HSCT (24 vs. 8 months, respectively). They proved allo-HSCT to be an independent predictor of outcome, although we must bear in mind that only a relatively small percentage of sAML patients can undergo the procedure. In our study group, only nine patients underwent allo-HSCT, but their median OS (18.8 months) was significantly higher compared to the rest of the patients, and comparable to that in the abovementioned literature [18].

Nevertheless, it remains controversial as to whether sAML is an independent prognostic factor on its own, or only through its correlation with other risk factors [5, 18]. Many studies have shown that the prognosis of sAML is similar to *de novo* AML with an equal cytogenetic risk [22–24]. Also, ELN 2022 emphasized the importance of cytogenetics and mutational profile of AML cells, rather than the clinical history of antecedent disorders or chemo/radiotherapy, when considering prognostic factors and treatment approach [7].

Consistent with the results of the PETHEMA study, in our analysis, clinical and laboratory variables such as age, higher ECOG score, greater percentage of blasts infiltration, and hypoalbuminemia have proven to be independent prognostic factors for poorer survival [13].

Cytogenetic abnormalities like complex karyotype, 5q deletion, 7q deletion, and trisomy 8 have been reported as independent prognostic factors for worsening OS in sAML patients [15]. In our study, low-risk cytogenetics resulted in the longest survival (mOS not reached), and high-risk cytogenetics implied the poorest outcomes (mOS 2.8 months). However, this did not turn out to be a significant independent prognostic factor ($p = 0.1$, HR 1.48, 95% CI: 0.92–2.38), the main reason for which may be missing data (n = 44).

Recently, conventional 3 + 7 therapy has given way to CPX-351, which was approved by the Food And Drug Administration (FDA) in 2017 [25] and recommended by the European Society for Medical Oncology (ESMO) 2020 guidelines for the treatment of acute myeloid leukemia with myelodysplasia-related changes (MRC-AML) and tAML ≥60 years [26]. A randomized phase III trial involving a cohort of 309 patients comprising 54% with MDS/MPN-AML, 21% tAML, and 25% with myelodysplasia-related

cytogenetic abnormalities, demonstrated the superiority of that therapy over a 3 + 7 regimen (mOS 9.6 vs. 5.9 months, composite complete remission (CRc) 47.7% vs. 33.3%, respectively) [27].

In practice, CPX-351 gives many clinical benefits, yet nevertheless is associated with prolonged cytopenia as well as longer hospitalization [28]. There is a need for further therapeutic improvements, including ongoing clinical trials that are testing the combination of CPX-351 with other drugs, such as cladribine, or targeted therapies, like FLT3 or IDH inhibitors. In our analysis, only 28% of MDS/MPN-AML and 16% of tAML patients were able to receive intensive treatment, yet it significantly improved their survival (13.8 vs. 2.4 months, p <0.00) and turned out to be a favorable prognostic factor.

We must acknowledge the fact that these patients were predominantly younger (only 30% were 60 or older) and this, alongside better ECOG, certainly had an additional positive impact on the prognosis.

For unfit patients, the use of hypomethylating agents (HMA) is usually the preferred therapy. Azacitidine seems to have a good impact, even in poor-risk cytogenetics or *TP53* mutations (encountered in as many as a third of tAML and MPN-AML cases) [29, 30]. In one single-center cohort study, HMA had an advantage over cytarabine-based regimens in terms of CR rates and CR duration and significantly extended mOS (9 vs. 5 months, p = 0.019) [30]. HMA might overcome some of the chemoresistance in the hypomethylating mechanism of tumor suppressor genes, leading to their re-expression, but the incomplete destruction of blast cells results in short responses and frequent relapses. A combination therapy of HMA and venetoclax has been proven to accelerate the achievement of treatment response and prolong survival in patients with unfavorable cytogenetic prognoses [31]. Another study conducted on a population of 145 unfit patients evaluated the efficacy and safety of venetoclax and HMA. This showed beneficial effects in patients with sAML and high cytogenetic risk. The median OS for all patients was 17.5 months, while the overall response rates [CR + CR with incomplete blood count recovery (CRi) + partial remission (PR)] were 76% for venetoclax + azacitidine (VEN/AZA) and 71% for venetoclax + decitabine [32, 33]. DiNardo et al. [34] also confirmed that VEN/AZA was superior to AZA alone by improving both median OS and CRc in sAML patients.

There are also reports of the effectiveness of venetoclax with low-dose cytarabine. A multicenter phase Ib/II study of 82 patients ineligible for intensive chemotherapy, of whom 49% were diagnosed with sAML, showed the efficacy of such therapy, with 54% of patients achieving CR/CRi, while the median OS was 10 months [35].

Taking into consideration the two main therapeutic approaches in sAML, Matthews et al. [36] compared CPX-351 versus VEN/AZA in a study of 656 AML patients (439 in the VEN/AZA arm and 217 in CPX-351). In the VEN/AZA group, 49% of patients had a diagnosis of sAML (n = 213), while in the CPX-351 group the figure was 71% (n = 154). Median OS for all patients was 12 months; 13 months for CPX-351 versus 11 months for VEN/AZA (p = 0.22). However, VEN/AZA patients were significantly older (median age 75 vs. 65-years-old; p <0.01) and fewer VEN/AZA patients received allo-HSCT compared to CPX-351 (10% vs. 28%, respectively; p <0.0005) [36]. This does not conclusively resolve the superiority of one therapy over the other, especially considering only patients with sAML, mainly due to differences between study groups, lack of randomization, and inconsistent inclusion criteria. However, differences in the primary endpoint have not been demonstrated, and thus the therapeutic approach should be individualized for each patient.

In our study, unfit patients were treated with AZA, LD-Ara-C, or qualified only to cytoreduction or BSC alone. In the analyzed period, venetoclax and CPX-351 were not approved and available. It is possible that the addition of venetoclax might improve the treatment results in that group, as both drugs are now available in Poland for AML patients.

Nevertheless, new therapeutic options are on the horizon. There are some histone deacetylase inhibitors tested in AML, such as panobinostat and vorinostat, yet there is no data for specific advantages of their usage in sAML [31]. As reported in one study, a combination of vorinostat with cytarabine and etoposide did not result in an increased response rate in a cohort of patients with relapsed/refractory (r/r) AML or sAML [37, 38]. Another agent in the early investigational phase is pinometostat, which may play a role in indirectly inhibiting the oncogenic effects of *KMT2A* — a common mutation in tAML. However, the hypothetical advantages of these drugs' application in sAML remain to be tested [31].

Some novel agents that could have an impact on sAML are currently being studied in clinical trials in combination or alone. Great expectations rest on the use of immune check-points [nivolumab (NCT02532231), pembrolizumab (NCT04284787)], *IDH* inhibitors — ivosidenib (NCT03173248, NCT02632708), enasidenib (NCT02632708), and targeted drugs for spliceosomes (NCT04278768) or bromodomain and extra-terminal domain (BET) proteins — NCT02698189, which unfortunately was terminated due to limited efficacy [2]. The literature indicates that therapy with chimeric antigen receptor-T (CAR-T) may also play a role in sAML [39–41].

Conclusions

Regardless of the increasing understanding of AML biology and the more accurate description of prognostic factors based on genetic mutations, the prognosis for patients with MDS/MPN-AML and tAML remains poor. Contributing

factors include unfavorable cytogenetic risk, a specific dysplasia-related mutational profile, and older age in the MDS/MPN-AML group, as well as the effects of preceding malignancy or prior treatment in patients with tAML.

Although the positive impact of intensive chemotherapy with subsequent allo-HSCT is marked in sAML patients, a therapeutic approach based on more personalized treatment may provide a better outcome. Therefore, there is no doubt that further progress is needed in optimizing treatment and in better understanding the biology of sAML, both at the clinical and molecular levels.

Authors' contributions

PS, MC, AP — creating the study protocol. PS, KMK and SS — patient enrolment and data acquisition. PS, DM — data analysis and statistics. PS and KMK — writing the manuscript. AW, AP and MC — manuscript revision and proofreading.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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