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Outcomes and prognostic factors in patients with systemic mastocytosis and an associated myeloid neoplasm: an international ECNM registry study

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Abstract

Background Systemic mastocytosis (SM) is a spectrum of hematologic disorders characterized by accumulation of atypical mast cells (MCs) in extracutaneous organs. SM with an associated hematologic neoplasm (SM-AHN), the most frequent subtype of advanced SM, is predominantly associated with myeloid neoplasms, consistent with shared clonal architecture. Because of its rarity and heterogeneity, robust outcome data aligned with contemporary classifications are needed to inform risk stratification.

Methods We analyzed the 10th data wave of the European Competence Network on Mastocytosis registry (34 European centers and 1 US center). SM and AHN diagnoses followed the 2022 World Health Organization classification. Baseline characteristics and overall survival (OS) were compared between patients with myeloid SM-AHN and SM without AHN (SM-no-AHN). Within SM-AHN, outcomes were analyzed by SM component (advanced:

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aggressive SM [ASM] or MC leukemia [MCL] vs. non-advanced: bone marrow mastocytosis, indolent SM, or smoldering SM) and AHN subtype.

Results Among 3,925 patients with SM, 467 (11.9%) had myeloid SM-AHN. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) were the most frequent AHN category (41.1%), with chronic myelomonocytic leukemia as the most common subtype (29.6%). Compared with SM-no-AHN, SM-AHN patients were older, more often male, and less frequently had skin involvement. The SM component was advanced in 55.0% of SM-AHN versus 5.8% of SM-no-AHN ($p < 0.001$). OS was shorter in SM-AHN than SM-no-AHN (median 36.1 vs. 340.9 months; $p < 0.001$) and was reduced across SM subtypes, including ASM (31.0 vs. 81.1 months) and MCL (7.1 vs. 23.2 months). Within SM-AHN, advanced SM-AHN had shorter OS than non-advanced SM-AHN (28.3 vs. 70.9 months; $p < 0.001$). Median OS differed by AHN subtype (57.0 months in SM–MPN, 35.7 in SM–MDS, 34.2 in SM–MDS/MPN, and 14.7 in SM associated with acute myeloid leukemia; $p < 0.001$). In multivariable analysis, non-advanced SM (vs. advanced) remained independently associated with improved OS (hazard ratio = 0.44; $p < 0.001$).

Conclusions SM-AHN is associated with reduced survival compared with SM without AHN across SM subtypes. Outcomes in SM-AHN are driven primarily by the aggressiveness of the mastocytosis component, supporting recognition and classification of SM in patients with concomitant myeloid neoplasms, given approved KIT-targeted tyrosine kinase inhibitors for advanced SM.

Keywords Systemic mastocytosis, SM-AHN, Associated myeloid neoplasm, Chronic myelomonocytic leukemia, Acute myeloid leukemia, Overall survival, KIT D816V

Introduction

Systemic mastocytosis (SM) encompasses a heterogeneous group of hematologic neoplasms characterized by the accumulation of atypical mast cells (MCs) in extracutaneous organs, particularly the bone marrow (BM) [1, 2]. In around 90% of all patients with SM, neoplastic cells (MCs and others) carry a point mutation in the *KIT* gene (primarily D816V) [3]. The International Consensus Classification (ICC) and the World Health Organization (WHO)'s 2022 classification distinguish three main categories of mastocytosis: (i) cutaneous mastocytosis, (ii) MC sarcoma, and (iii) systemic mastocytosis (SM), by far the most common form in adults [4–6]. Several subtypes of SM have been described, depending on organ involvement and the aggressiveness of the disease. Non-advanced SM (non-Adv-SM) includes bone marrow mastocytosis (BMM), indolent SM (ISM), and smoldering SM (SSM), whereas advanced SM (Adv-SM) includes aggressive SM (ASM), MC leukemia (MCL) and SM with an associated hematologic neoplasm (SM-AHN), the most frequent variant of Adv-SM in adults.

Several articles have reported on the epidemiology of SM-AHN and associated outcomes [7–11]. In the study by Lim et al., 89% of the cases of AHN were of myeloid origin, with myeloproliferative neoplasms (MPNs) and chronic myelomonocytic leukemia (CMML) being the most frequent AHN subtypes (45% and 29%). Transformation to acute myeloid leukemia (AML) was observed frequently (29%) in patients with SM associated with myelodysplastic neoplasms (MDS). The patients' median overall survival (OS) was found to depend on the type of AHN: OS was significantly longer in SM-MPN (31 months) than in other types of myeloid neoplasms, including CMML, MDS and AML (15, 13 and 11 months, respectively; $p = 0.003$). In a collaboration between the European Competence Network on Mastocytosis (ECNM) and the Spanish *Red Española de Mastocitosis* network, 174 SM-AHN patients (27.9% SM-CMML) were assessed. The overall median OS was 2.9 years, with SM-AML showing the poorest outcomes among SM-AHN subtypes [10].

Beyond *KIT*, SM-AHN is characterized by additional genetic alterations recurrently observed in myeloid neoplasms (e.g., *TET2*, *SRSF2*). Some genetic events are associated with specific AHN subtypes (e.g., *JAK2* mutations in conventional MPNs), whereas other mutations are associated with poor prognosis (such as *SRSF2*, *ASXL1*, and *RUNX1*; S/A/R) [8, 12–16]. Studies of the clonal architecture have frequently revealed a common clonality between SM and AHN components, with the exception of the *JAK2* V617F mutation [17, 18]. These findings explain the over-representation of myeloid neoplasms vs. lymphoid neoplasms that may not share clonality in most cases [19, 20]. Thus, in contrast to the WHO classification, the ICC recommends classifying associated BM diseases only in cases presenting with an associated myeloid neoplasm (AMN) [6]. In addition, the ICC and the WHO classification now recommend specifying the subtype of SM component: for example, if the SM component is indolent, the patient should be classified as ISM-AHN.

To date, SM-AHN outcomes have mostly been reported in mixed cohorts, and the respective prognostic impact of the SM component (advanced vs. non-advanced) and the associated myeloid neoplasm subtype remains incompletely defined within current WHO/ICC frameworks, likely because large sample sizes are required

for adequately powered subgroup analyses. Moreover, accurate recognition of advanced SM is increasingly relevant in the era of approved KIT-targeted therapies for advanced SM [12, 13]. To address these gaps, we conducted a multinational real-world study using the international ECNM registry, analyzing the largest reported cohort of patients with myeloid SM-AHN and comparing them with patients with SM without an associated hematologic neoplasm (SM-no-AHN) [21].

Methods

The study participants and the ECNM registry

We included all patients diagnosed with SM from the 10th data wave of the ECNM registry, which relates to patients with mastocytosis in 34 centers in Europe and one center in the United States (Stanford Cancer Institute). The patient cohorts included SM-AHN from myeloid origin and control patients with SM without AHN (SM-no-AHN, including ISM, BMM, SSM, ASM, and MCL) [22]. Patients who developed an AHN during follow-up were classified in the SM-AHN group. The study design adhered to the tenets of the Declaration of Helsinki and was approved by the investigating centers' respective institutional review boards. Before inclusion in the ECNM registry, all patients provided their written, informed consent, and their inclusion complied with the standards of the corresponding local institutional review board. This study is reported in accordance with the STROBE guideline and the RECORD extension for studies using routinely collected health data. The ECNM registry data are captured using Datamedrix software Clinspire and are stored at ANEXIA (http://ecnm.clinspire.at/).

Diagnosis

All patients (including SM and AHN components) were diagnosed according to the WHO 2022 classification [4, 5]. Within SM-AHN, we distinguished patients according to the aggressiveness of the SM component: advanced SM-AHN (Adv-SM-AHN) refers to patients whose SM component is ASM or MCL, whereas non-advanced SM-AHN (non-Adv-SM-AHN) refers to patients whose SM component is BMM, ISM, or SSM. These terms describe the SM component within the composite SM-AHN diagnosis and should not be confused with the broader WHO category of advanced SM, which by definition includes all SM-AHN regardless of the SM component subtype. MDS included MDS with < 5% blasts and ≥ 5% blasts in BM smear. MPN included polycythemia vera (PV), essential thrombocythemia (ET), chronic myeloid leukemia (CML), chronic eosinophilic leukemia (CEL), primary myelofibrosis (PMF), and MPN not otherwise specified (MPN-NOS). MDS/MPN included CMML, atypical CML (a-CML), and MDS/MPN not otherwise specified (MDS/MPN-NOS).

Clinical and laboratory data collection

Clinical and laboratory variables were captured at diagnosis and/or during follow-up: age, sex, the WHO-based final diagnosis (according to the 2022 guideline), the presence of the WHO classification's major and minor diagnostic criteria, a complete blood count, serum biochemistry, basal serum tryptase (BST), the percentage of MCs on BM biopsy sections, the flow cytometry (FC)- or immunohistochemistry (IHC)-based phenotype of the MCs, molecular and cytogenetic data. We collected the presence of B findings including hepatomegaly, splenomegaly (defined as palpable hepatomegaly or splenomegaly), lymphadenopathy (> 2 cm) and dysmyelopoiesis and C findings including weight loss (defined as > 10% weight loss over the previous 12 months), malabsorption, ascites, portal hypertension, large osteolytic lesions and/or pathologic fractures. Variables of interest were also the presence of mediator-related symptoms, including skin symptoms, itching, blistering, flushing, osteoporosis, bone pain, anaphylaxis, gastrointestinal symptoms (diarrhea, cramping, gastric ulcers, or duodenal ulcers), cytoreductive therapy, progression of both the SM component (defined as a change in the SM diagnosis, i.e. from ISM/BMM to SMM or from ISM/BMM/SSM to ASM/MCL or from ASM to MCL) and the AHN component (AML transformation), the date of last follow-up, and the date of death (if applicable).

Statistical analysis

We described quantitative variables with median, interquartile range (IQR) and range, and discrete variables with counts and percentages. Categorical variables were compared using the Chi-square test, while continuous variables were assessed using the Mann–Whitney U test. Logistic regression was used to assess associations between variables (see Supplementary Methods section for details). Univariate survival analyses were performed using the Kaplan-Meier method to estimate survival probabilities, and the log-rank test was used to compare survival curves between groups. Additionally, a multivariable analysis was performed using Cox proportional hazards regression to assess the independent effect of the covariates on the primary outcome, adjusting for potential confounders identified a priori. Proportional hazards assumptions were confirmed for all covariates in the Cox regression models. All statistical tests were two-tailed, and a P-value less than 0.05 was considered statistically significant. Data were analyzed using R statistical software, version 4.2.2.

Table 1 General characteristics, laboratory parameters, and outcomes for patients with non-Adv-SM-AHN vs. Adv-SM-AHN

	Non-Adv-SM-AHN (*n* = 210)	Adv-SM-AHN (*n* = 257)	*P*-value[1]
General characteristics			
Sex Male (%)	123/210 (58.6%)	186/257 (72.4%)	0.002
Median [IQR] Age	66.0 [54.2 ; 72.0]	67.0 [62.0 ; 73.0]	0.010
Median [IQR] BMI	25.4 [23.4 ; 28.4]	24.6 [22.2 ; 26.8]	0.012
Median [IQR] Performance status	1 [0 ; 1]	1 [1 ; 2]	0.001
Diagnosis			
AHN subtype			0.001[2]
AML (%)	35/210 (16.7%)	20/257 (7.8%)	
MPN (%)	81/210 (38.6%)	60/257 (23.3%)	
CML (%)	6/210 (2.9%)	1/257 (0.4%)	
PV (%)	13/210 (6.2%)	0/257 (0.0%)	
ET (%)	27/210 (12.9%)	4/257 (1.6%)	
PMF (%)	15/210 (7.1%)	16/257 (6.2%)	
MPN-NOS (%)	13/210 (6.2%)	22/257 (8.6%)	
CEL (%)	7/210 (3.3%)	17/257 (6.6%)	
MDS (%)	42/210 (20.0%)	37/257 (14.4%)	
MDS < 5% blasts (%)	29/210 (13.8%)	20/257 (7.8%)	
MDS ≥ 5% blasts (%)	13/210 (6.2%)	17/257 (6.6%)	
MDS/MPN (%)	52/210 (24.8%)	140/257 (54.5%)	
CMML (%)	41/210 (19.5%)	97/257 (37.7%)	
MDS/MPN-NOS (%)	8/210 (3.8%)	39/257 (15.2%)	
a-CML (%)	3/210 (1.4%)	4/257 (1.6%)	
Diagnostic characteristics			
MC-infiltrates present in BM biopsy (%)	180/193 (93.3%)	241/249 (96.8%)	0.084
Median % [IQR] of BM MC infiltrates*	10.0 [5.0 ; 21.7]	30.0 [15.0 ; 50.0]	0.001
Median % [IQR] of spindle shaped MC in BM*	30.0 [25.0 ; 80.0]	50.0 [29.6 ; 90.0]	0.128
MC present in smears (%)	102/163 (62.6%)	122/190 (64.2%)	0.751
Median % [IQR] of MC in BM smears.	2.5 [1.0 ; 8.0]	6.0 [2.0 ; 20.0]	0.001
CD2 expression present on BM MC** (%)	69/126 (54.8%)	54/137 (39.4%)	0.013
CD25 expression present on BM MC** (%)	157/166 (94.6%)	185/190 (97.4%)	0.177
CD30 expression present on BM MC** (%)	26/49 (53.1%)	42/56 (75.0%)	0.019
Well differentiated morphology of MC present (%)	7/80 (8.8%)	4/67 (6.0%)	0.523
KIT D816V mutation present in BM/PB (%)	146/179 (81.6%)	221/228 (96.9%)	< 0.001
KIT D816V mutation allele burden (%)	19.0 [1.4 ; 38.2]	28.0 [11.7 ; 41.9]	0.132
JAK2 V617 mutation present in BM/PB (%)	45/110 (40.9%)	18/120 (15.0%)	< 0.001
MPL mutation present in BM/PB (%)	2/107 (1.9%)	4/117 (3.4%)	0.473
CALR mutation present in BM/PB (%)	3/107 (2.8%)	0/116 (0.0%)	0.069
S/A/R mutation(s) present(s) in BM/PB (%)	32/73 (43.8%)	75/100 (75.0%)	< 0.001
Cytogenetic abnormality*** (%)	27/117 (23.1%)	22/141 (15.6%)	0.128
Clinical characteristics			
Mastocytosis skin involvement (%)	75/203 (36.9%)	85/251 (33.9%)	0.494
Splenomegaly (%)	69/189 (36.5%)	194/237 (81.9%)	< 0.001
Hepatomegaly (%)	43/185 (23.2%)	151/234 (64.5%)	< 0.001
Lymphadenopathy (%)	17/172 (9.9%)	105/191 (55.0%)	< 0.001
Dysmyelopoiesis (%)	95/190 (50.0%)	198/235 (84.3%)	< 0.001
Osteolysis (%)	2/157 (1.3%)	13/189 (6.9%)	0.011
Ascites (%)	6/174 (3.4%)	102/229 (44.5%)	< 0.001
Portal hypertension (%)	2/174 (1.1%)	34/182 (18.7%)	< 0.001
Malabsorption (%)	2/184 (1.1%)	60/212 (28.3%)	< 0.001
Weight loss (≥ 10% within last 12 months) (%)	13/186 (7.0%)	152/240 (63.3%)	< 0.001
Laboratory variables			
Median BST (ng/ml) [IQR]	52.4 [26.0 ; 127.8]	186.0 [105.7 ; 310.3]	0.001
Median WBC count (G/L) [IQR]	7.5 [4.0 ; 11.5]	11.0 [5.3 ; 20.8]	0.001

Table 1 (continued)

	Non-Adv-SM-AHN (*n* = 210)	Adv-SM-AHN (*n* = 257)	*P*-value[1]
Median neutrophils count (G/L) [IQR]	3.9 [1.8 ; 6.3]	5.5 [2.6 ; 11.2]	0.001
Median eosinophils count (G/L) [IQR]	0.2 [0.0 ; 0.5]	0.4 [0.1 ; 1.6]	0.001
Median monocytes count (G/L) [IQR]	0.6 [0.3 ; 1.1]	1.3 [0.6 ; 2.3]	0.001
Median basophils count (G/L) [IQR]	0.0 [0.0 ; 0.1]	0.0 [0.0 ; 0.2]	0.674
Median lymphocytes count (G/L) [IQR]	1.8 [1.2 ; 2.5]	1.5 [0.9 ; 2.2]	0.019
Median hemoglobin (g/dl) [IQR]	11.8 [9.6 ; 13.8]	10.2 [8.9 ; 11.8]	< 0.001
Median platelet count (G/L) [IQR]	195.5 [93.8 ; 382.9]	93.5 [59.4 ; 168.2]	< 0.001
Median LDH (IU/L) [IQR]	202.8 [156.4 ; 288.0]	199.0 [148.9 ; 271.1]	0.319
Median ALP (IU/L) [IQR]	89.8 [69.2 ; 131.6]	228.5 [131.8; 412.0]	< 0.001
Median albumin (g/L) [IQR]	42.0 [38.8 ; 46.0]	38.0 [32.8 ; 41.0]	< 0.001
Median ß2-Micro-globulin (mg/L) [IQR]	2.9 [2.2 ; 3.7]	4.1 [3.1 ; 5.2]	< 0.001
Outcomes			
Transformation to AML (%)	17/151 (11.3%)	31/232 (13.4%)	0.543
Time to transformation to AML (months)	7.1 [1.8 ; 38.3]	20.4 [8.5 ; 31.7]	0.220
Patient death (%)	76/183 (39.0%)	194/250 (76.8%)	< 0.001
Cause of death			0.083
Disease-related (%)	49/68 (72.1%)	142/177 (80.2%)	
Treatment-related (%)	3/68 (4.4%)	13/177 (7.3%)	
Other (%)	16/68 (23.5%)	22/177 (12.4%)	

Non-Adv-SM-AHN: Non-advanced systemic mastocytosis with an associated hematologic neoplasm. Adv-SM-AHN: Advanced systemic mastocytosis with an associated hematologic neoplasm. IQR: Interquartile range. AML: Acute myeloid leukemia. MDS: Myelodysplastic neoplasms. MPN: Myeloproliferative neoplasms. CML: chronic myeloid leukemia. ET: essential thrombocytosis. PMF: primary myelofibrosis. PV: polycythemia vera. MPN-NOS: MPN not otherwise specified. CEL: chronic eosinophilic leukemia. CMML: chronic myelomonocytic leukemia. MDS/MPN-NOS: MDS/MPN not otherwise specified. a-CML: atypical CML. BST: Basal serum tryptase. WBC: White blood cell. ALP: Alkaline phosphatase. BM: Bone marrow. PB: Peripheral blood. MC: Mast cell. S/A/R: *SRSF2, ASXL1, RUNX1*. *By immunohistochemistry. **By immunohistochemistry and/or flow cytometry. ***Somatic cytogenetic abnormality except -Y. [1]Statistical tests performed: chi-squared test of independence; Mann–Whitney U test. [2]$p < 0.001$ for comparison of AHN groups and AHN diagnoses between Adv-SM-AHN and non-Adv-SM-AHN groups

Results

Patients and diagnoses

Overall, 3,925 patients with SM were identified, including 467 (11.9%) with SM-AHN of myeloid origin diagnosed between April 1988 and February 2025, among whom 61 developed the AHN during SM follow-up. The most frequent AHN category was MDS/MPN (41.1%), with CMML being the most common subtype (29.6% of all AHN cases). Other AHN categories included MPN (30.2%), MDS (16.9%; including 6.4% with ≥ 5% blasts), and AML (11.8%, Supplementary Table 1). The SM component was advanced in 257/467 (55.0%) patients (ASM, $n = 236$; MCL, $n = 21$) and non-advanced in 210/467 (45.0%) patients (BMM, $n = 35$; ISM, $n = 159$; SSM, $n = 16$).

Clinical characteristics and laboratory variables in patients with SM-AHN and SM-no-AHN

The SM-AHN and SM-no-AHN patients differed with regard to several clinical and laboratory variables (Supplementary Table 2). SM-AHN patients were older (median age: 67 vs. 48 years; $p < 0.001$) and more frequently male (66.2% vs. 43.8%; $p < 0.001$). The SM component was more likely to be advanced in patients with SM-AHN than in patients with SM-no-AHN (55.0% vs. 5.8%; $p < 0.001$). Among patients with an Adv-SM component, ASM was more prevalent in those with SM-AHN compared to those without AHN (91.8% vs. 73.4%; $p < 0.001$). The prevalence of mastocytosis skin involvement was lower in SM-AHN than in SM-no-AHN (35.2% vs. 70.8%, respectively; $p < 0.001$). All B- and C-findings were more common in SM-AHN patients compared to SM-no-AHN patients. In contrast, most symptoms (including cutaneous, cardiovascular, osteopenia, headache, and allergic symptoms) were more frequent in SM-no-AHN patients than in those with SM-AHN.

Median basal serum tryptase (BST) levels were higher in SM-AHN patients than in SM-no-AHN patients (127.0 vs. 31.0 ng/mL, respectively; $p < 0.001$). Median white blood cell (WBC) counts were also higher in SM-AHN patients (9.0 vs. 6.5 G/L, respectively; $p < 0.001$), while both hemoglobin levels and platelet counts were lower compared to SM-no-AHN patients. Alkaline phosphatase (ALP) levels in SM-AHN patients were nearly twice those observed in SM-no-AHN patients (137.0 vs. 73.0 IU/L, respectively; $p < 0.001$), and serum albumin levels were significantly lower (39.6 vs. 44.0 g/L, respectively; $p < 0.001$). BM assessment using immunohistochemistry (IHC) showed that the median MC infiltration percentage was higher in SM-AHN patients than in SM-no-AHN patients (20.0% vs. 10.0%, respectively; $p < 0.001$). CD2 expression on MCs, detected by IHC or flow cytometry (FC), was less frequent in SM-AHN compared to SM-no-AHN patients (46.8% vs. 76.8%, respectively; $p < 0.001$), whereas CD30 expression on MCs was more frequent

in SM-AHN (64.8% vs. 51.9%; $p = 0.014$). Additionally, well-differentiated MC morphology was less prevalent in SM-AHN than in SM-no-AHN patients (7.5% vs. 26.2%; $p < 0.001$). The *KIT* D816V mutation in BM or peripheral blood (PB) was similarly detected in both groups (90.2% vs. 87.5%; $p = 0.120$).

In multivariable analysis, male sex (OR = 1.80; $p < 0.001$), older age (OR = 1.80; $p < 0.001$), and absence of cutaneous mastocytosis (OR = 0.47; $p < 0.001$) were independently associated with the presence of AHN (Supplementary Table 3). Finally, the presence of an Adv-SM component was strongly associated with the presence of an AHN component (OR = 2.66, $p < 0.001$).

Clinical characteristics and laboratory variables in patients with Adv-SM-AHN and non-Adv-SM-AHN

Patients with Adv-SM-AHN, [i.e., ASM-AHN or MCL-AHN], ($n = 257$) were slightly older than those with non-Adv-SM-AHN, [i.e., BMM-AHN, ISM-AHN, or SSM-AHN], ($n = 210$; 67 vs. 66 years; $p = 0.010$) and more frequently male (72.4% vs. 58.6%; $p = 0.002$, Table 1). The distribution of AHN subtypes differed between groups: AML and MPN were more frequent in non-Adv-SM-AHN than in Adv-SM-AHN (16.7% vs. 7.8% for AML, $p = 0.003$; and 38.6% vs. 23.3% for MPN, $p < 0.001$), whereas MDS/MPN was more common in Adv-SM-AHN (54.5% vs. 24.8%; $p < 0.001$).

Clinical and laboratory features varied markedly according to the aggressiveness of the SM component (Table 1). Adv-SM-AHN was associated with higher rates of splenomegaly, hepatomegaly, and lymphadenopathy, while skin involvement was similar between groups (33.9% vs. 36.9%; $p = 0.494$). Median basal serum tryptase (BST) levels were higher in Adv-SM-AHN patients than in non-Adv-SM-AHN patients (186.0 vs. 52.4 ng/mL; $p < 0.001$), as were ALP levels (228.5 vs. 89.8 IU/L; $p < 0.001$). Median hemoglobin levels and platelet counts were both lower in Adv-SM-AHN patients compared to non-Adv-SM-AHN patients (10.2 vs. 11.8 g/dL, $p < 0.001$; and 93 vs. 195 G/L, $p < 0.001$). The median BM MC infiltration assessed by immunohistochemistry (IHC) was higher in Adv-SM-AHN (30.0% vs. 10.0%; $p = 0.001$). CD2 expression on MCs was less frequent in Adv-SM-AHN (39.4% vs. 54.8%; $p = 0.013$), whereas CD30 expression was more frequent (75.0% vs. 53.1%; $p = 0.019$). *KIT* D816V was detected more frequently in BM and/or peripheral blood (PB) in Adv-SM-AHN (96.9% vs. 81.6%; $p < 0.001$), while *KIT* D816V variant allele frequency (VAF) did not differ significantly (28.0% vs. 19.0%; $p = 0.132$). *JAK2* V617F was more frequent in non-Adv-SM-AHN (40.9% vs. 15.0%; $p < 0.001$), whereas S/A/R mutations were more prevalent in Adv-SM-AHN (75.0% vs. 43.8%; $p < 0.001$).

In multivariable analysis (Supplementary Table 4), an AML diagnosis was independently associated with non-Adv-SM-AHN (OR = 0.27; $p = 0.004$). Among laboratory variables, lower hemoglobin and platelet counts and higher BST and ALP levels were independently associated with an advanced SM component (OR = 0.80 per 1 g/dL increase in hemoglobin, $p = 0.002$; OR = 0.84 per 100 G/L increase in platelet count, $p = 0.034$; OR = 1.50 per doubling of BST, $p < 0.001$; and OR = 1.53 per doubling of ALP, $p = 0.002$).

Comparison of survival between SM-AHN and SM-no-AHN patients

Over a median follow-up of 24.9 months for SM-AHN patients and 65.3 months for SM-no-AHN patients, 270/433 (62.4%) SM-AHN patients and 160/2548 (5.8%) SM-no-AHN patients died ($p < 0.001$). The median OS was significantly shorter in SM-AHN patients compared to SM-no-AHN patients (36.1 vs. 340.9 months; $p < 0.001$, Fig. 1A). Of note, the SM component was advanced in 55.0% of SM-AHN versus 5.8% of SM-no-AHN patients ($p < 0.001$). To account for this imbalance, SM subtype–stratified survival comparisons were performed and are presented in Supplementary Figs. 2–6. The adverse impact of AHN on OS was observed in patients with a non-advanced SM component (median OS: 70.9 months for SM-AHN vs. 340.9 months for SM-no-AHN; $p < 0.001$, Supplementary Fig. 1A) and in those with an advanced SM component (28.3 months for SM-AHN vs. 76.8 months for SM-no-AHN; $p < 0.001$, Supplementary Fig. 1B). Consistently, the presence of an AHN was associated with lower OS compared to SM-no-AHN across all SM subtypes (ASM, MCL, ISM, BMM, and SSM; Supplementary Figs. 2–6).

Survival of patients with SM-AHN as a function of the SM component and AHN subtype

Among SM-AHN patients, the Adv-SM component was associated with a higher mortality rate (76.8% vs. 39.0% for the non-Adv-SM-AHN group, $p < 0.001$; Table 1) and a shorter median OS (28.3 months vs. 70.9 months in non-Adv-SM-AHN patients, $p < 0.001$; Fig. 1B). In SM-AHN, median OS was longer in SM-MPN (57.0 months) than in SM-MDS or SM-MDS/MPN (35.7 and 34.2 months), whereas SM-AML had the poorest outcome (14.7 months; $p < 0.001$; Fig. 2A). However, among Adv-SM-AHN patients, median OS differed significantly only for SM-AML ($p < 0.001$; Fig. 2B). Finally, *JAK2* V617F positivity was associated with longer OS (median 110.4 vs. 35.7 months; $p < 0.001$), while the presence of one or more S/A/R mutations was associated with shorter OS (median 34.3 vs. 56.2 months; $p = 0.003$; Supplementary Fig. 7A–B).

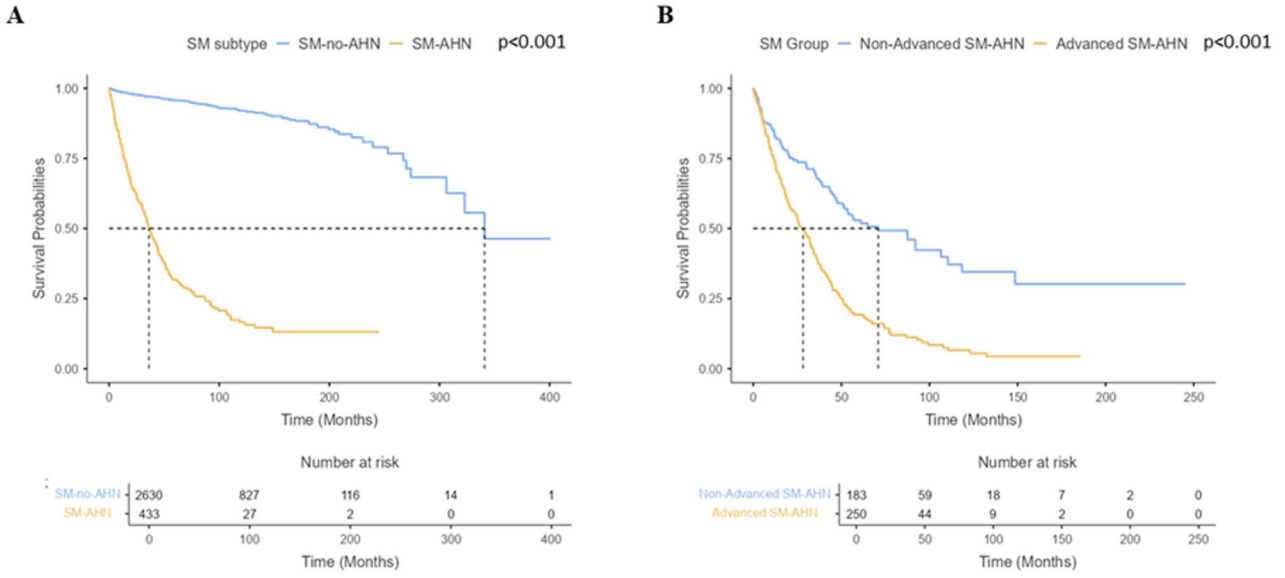


Fig. 1 Overall survival in systemic mastocytosis according to associated hematologic neoplasm status and SM subtype (advanced vs. non-advanced). (**A**) Overall survival in SM-AHN patients ($n = 433$) vs. SM-no-AHN patients ($n = 2630$). Median overall survival: 36.1 months in SM-AHN patients and 340.9 months, in SM-no-AHN patients. (**B**) Overall survival in Adv-SM-AHN patients ($n = 250$) vs. non-Adv-SM-AHN patients ($n = 183$). Median overall survival: 28.3 months in Adv-SM-AHN patients and 70.9 months in non-Adv-SM-AHN patients. P-value calculated by Log-rank test. Time in months

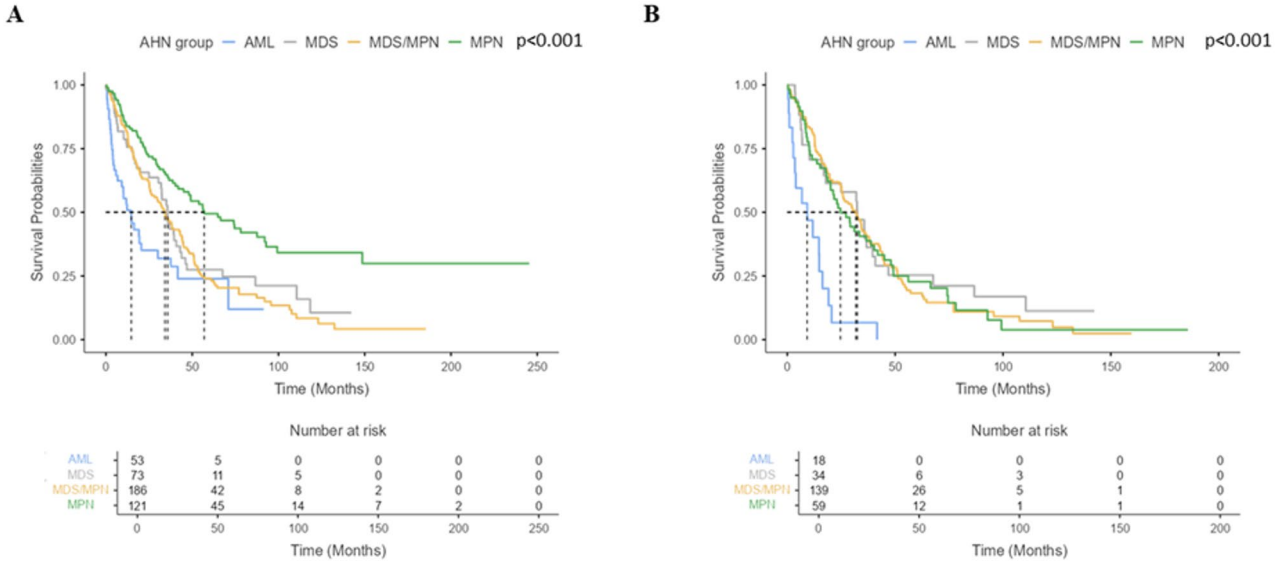


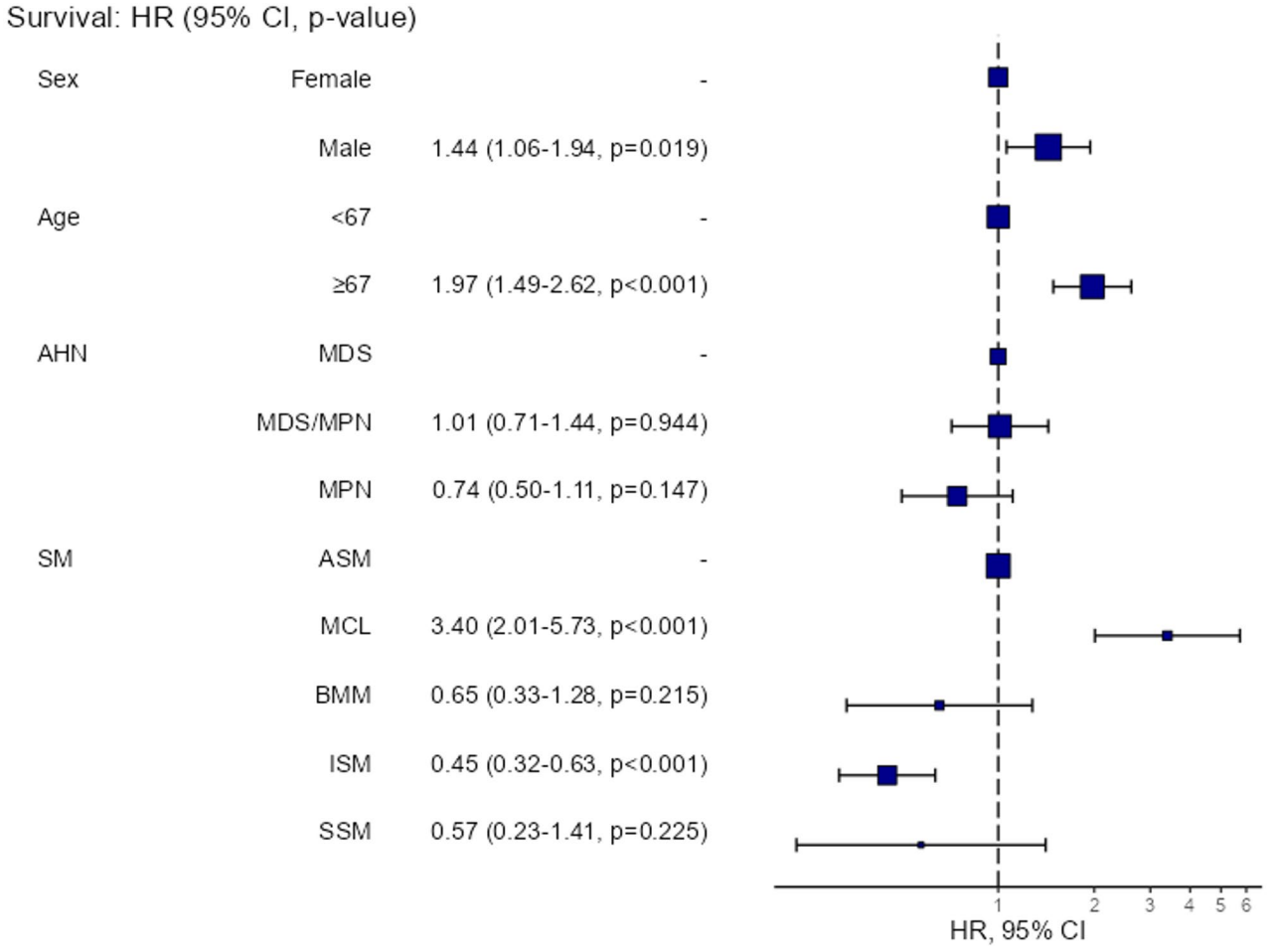
Fig. 2 Overall survival in SM-AHN according to associated myeloid neoplasm subtype in the overall and advanced SM-AHN cohorts. (**A**) Overall survival in SM-AHN patients according to AHN subtype. Median overall survival: 57.0 months in SM-MPN patients, 35.7 in SM-MDS patients, 34.2 months in SM-MDS/MPN patients and 14.7 months in SM-AML patients. (**B**) Overall survival in Adv-SM-AHN patients according to AHN subtype. Median overall survival: 24.6 months in Adv-SM-MPN patients, 32.5 months in Adv-SM-MDS patients 31.7 months in Adv-SM-MDS/MPN patients and 9.2 months in Adv-SM-AML patients. AML: Acute myeloid leukemia. MDS: Myelodysplastic neoplasms. MPN: Myeloproliferative neoplasms. P-value calculated by Log-rank test. Time in months

In multivariable analyses, the aggressiveness of the SM component (but not AHN subtypes other than AML) was significantly associated with OS (hazard ratio (HR) = 0.44 for non-Adv-SM vs. Adv-SM component, $p < 0.001$; Supplementary Table 5). Specifically, ISM was associated with improved OS (HR = 0.45, $p < 0.001$), whereas MCL was associated with inferior OS (HR = 3.4, $p < 0.001$; Table 2).

Progression of SM and AHN components

Overall, 32/432 (7.4%) patients with SM-AHN with available follow-up data on SM progression experienced progression of the SM component during a median follow-up

Table 2 Multivariable Cox proportional hazard survival analyses of factors related to overall survival in SM-AHN patients



Multivariable analysis (Cox model) of factors related to OS in SM-AHN patients according to the sex, age, SM subtype and AHN subtype. HR: hazard ratio. HR >1 indicate worse survival; HR <1 indicate better survival. SM: systemic mastocytosis. ASM: aggressive SM. MCL: mast cell leukemia. BMM: bone marrow mastocytosis. ISM: indolent SM. SSM: smoldering SM. AHN: associated hematologic neoplasms. MDS: Myelodysplastic neoplasms. MPN: Myeloproliferative neoplasms. We filtered out the patients with AML (violation of the proportionality assumption in the COX model)

of 24.9 months (Supplementary Table 6). SM progression occurred predominantly from ISM to ASM (13/32 progression events, 40.6%) and from ASM to MCL (12/32 progression events, 37.5%). Among the 12 ASM patients who progressed, all transformed to MCL. Regarding the AHN component, 48/383 (12.5%) SM-AHN patients with available follow-up data and at risk for transformation developed AML during follow-up (Supplementary Table 7). At the time of SM-AHN diagnosis, no significant differences were observed between patients with or without subsequent AML transformation in terms of age, sex, SM subtype, BM MC infiltration, BST, or B- and C-findings. However, AHN subtype was associated with AML transformation, with MDS being more frequent among patients who transformed to AML than among those who did not (33.3% vs. 17.0%; $p = 0.007$). Molecular features also differed between groups, with a lower frequency of *JAK2* V617F and a higher prevalence of S/A/R mutations among patients who transformed to AML. However, in multivariable analysis, only an MDS subtype remained significantly associated with AML transformation (OR = 2.21; $p = 0.034$; Supplementary Table 8).

Discussion

SM-AHN is the most common subtype of Adv-SM and includes many entities with variable SM and AHN components. Although a common clonal origin of SM- and AHN-related neoplastic stem cells and subsequent clonal diversity due to secondary mutations may explain the more frequent association between AHN of myeloid origin and SM, the link between specific AHN subtypes (i.e. MDS/MPN) and SM is not fully understood. Therefore, further research on the underlying disease mechanisms and the clinical impact of each SM-AHN subset and related clonal pattern is warranted to better define prognosis and therapeutic strategies.

Our results for the epidemiology of AHN were in line with the literature data [7–9]. Indeed, the most

frequently observed type of AHN was MDS/MPN, and especially CMML. Interestingly, CMML was more likely to be associated with an Adv-SM component. This overrepresentation might explain the previously reported worse survival in SM-CMML patients (relative to CMML patients) as death might sometimes be related to the progression of the SM component rather than the transformation to AML [23].

Patients with SM-AHN showed fewer typical clinical signs of mastocytosis (such as maculopapular skin lesions and MC activation symptoms) but more signs of hematologic neoplastic disorders (such as splenomegaly and lymphadenopathy). Given the risk of SM under-diagnosis and the impact of a diagnosis of SM on the patient's management, it might be useful to assay for BST level and *KIT* D816V mutation using droplet digital PCR in more patients with MPN and MDS/MPN neoplasms (particularly those with CMML) to diagnose all cases with SM-AHN. Indeed, in many patients with MDS/MPN, MPN, or AML, neoplastic MCs may be outnumbered by "AHN-type cells" so that the SM portion of the disease is overlooked.

In line with previous reports, we found that OS was shorter in SM-AHN patients than in SM-no-AHN patients. Even though the Adv-SM component is more prevalent in SM-AHN than in controls, the presence of an AHN worsens the prognosis in all SM subtypes (relative to SM-no-AHN). Furthermore, our data highlighted the critical need to specify the subtype of the SM component (as recommended by the international classifications), given its impact on survival [5, 6]. Indeed, we found that the median OS was significantly shorter in patients with Adv-SM-AHN than in non-Adv-SM-AHN. Furthermore, this association with poor survival was still statistically significant after adjustment for the AHN subtype (excluding AML). Consequently, the AHN subtype did not significantly modify the median OS in patients with Adv-SM-AHN. This observation highlights the importance of treating the SM component in these patients - either alone or together with treatment of the AHN. In contrast, the AHN subtype appeared to influence survival in non-Adv-SM-AHN patients. Prospective studies are required to determine the value of targeting the SM component in these subtypes (especially in patients with a non-advanced SM component and concomitant AML).

This study has limitations inherent to retrospective registry-based analyses. First, data were collected across multiple centers over a long time period, and some variables were missing or incompletely captured, leading to varying denominators across analyses and potential measurement error. Second, although diagnoses were reported according to the 2022 WHO classification, assessment of historical cases may have been influenced by evolving diagnostic practices and molecular testing availability, and centralized pathology review was not performed. In addition, some clinical findings (in particular, splenomegaly and dysmyelopoiesis, which are B-findings) may be attributable to the AHN rather than the SM component, and disentangling the respective contributions of each component to organ damage (C-findings) remains an inherent challenge in SM-AHN, relying on cytological features, tryptase levels, and KIT D816V variant allele frequency. However, all diagnoses in this study were established by expert investigators at ECNM reference centers using the 2022 WHO classification criteria. Third, the ECNM registry includes referral centers, which may introduce selection and ascertainment biases and limit generalizability. Fourth, because patients were enrolled over several decades, temporal ("era") effects may have influenced outcomes and were not formally modeled. In particular, the majority of patients in this cohort were diagnosed and managed before the widespread availability of KIT-targeting therapies for advanced SM, including midostaurin and avapritinib [24, 25]. Consequently, our survival estimates may not be fully generalizable to contemporary practice. Of note, data from prospective clinical trials suggest that selective KIT inhibitors may also favorably impact AHN-related features such as eosinophilia and monocytosis, further underscoring the importance of recognizing the SM component in patients with concomitant myeloid neoplasms. Fifth, the higher prevalence of an advanced SM component in the SM-AHN cohort compared with SM-no-AHN limits the interpretability of unadjusted global comparisons; however, SM subtype–stratified analyses consistently confirmed the adverse prognostic impact of the AHN component. Finally, despite multivariable adjustment, residual confounding cannot be excluded, and findings should be interpreted as observational associations.

Conclusions

In conclusion, SM-AHN is a highly heterogeneous entity in which both the SM and AHN components shape clinical presentation and outcome. In this large international ECNM registry study, prognosis within SM-AHN was driven primarily by the aggressiveness of the SM component, rather than by most AHN subtypes, with the expected exception of SM-AML. These findings support systematic recognition and precise classification of the SM component in patients presenting with a concomitant myeloid neoplasm, which is increasingly relevant in the era of approved KIT-targeted therapies for advanced SM.

Abbreviations

a-CML	Atypical chronic myeloid leukemia
Adv-SM	Advanced systemic mastocytosis
Adv-SM-AHN	Advanced systemic mastocytosis with an associated hematologic neoplasm
AHN	Associated hematologic neoplasm
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
AMN	Associated myeloid neoplasm
ASCT	Allogeneic stem cell transplantation
ASM	Aggressive systemic mastocytosis
BM	Bone marrow
BMM	Bone marrow mastocytosis
BST	Basal serum tryptase
CEL	Chronic eosinophilic leukemia
CI	Confidence interval
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
ECNM	European Competence Network on Mastocytosis
ET	Essential thrombocythemia
FC	Flow cytometry
HR	Hazard ratio
ICC	International Consensus Classification
IHC	Immunohistochemistry
IQR	Interquartile
ISM	Indolent systemic mastocytosis
MC	Mast cell
MCL	Mast cell leukemia
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MDS/MPN-NOS	Myelodysplastic/myeloproliferative neoplasms not otherwise specified
MDS	Myelodysplastic neoplasms
mIWG-MRT-ECNM	Modified International Working Group - Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis
MPN	Myeloproliferative neoplasms
MPN-NOS	Myeloproliferative neoplasms not otherwise specified
Non-Adv-SM	Non-advanced systemic mastocytosis
Non-Adv-SM-AHN	Non-advanced systemic mastocytosis with an associated hematologic neoplasm
OR	Odds ratio
OS	Overall survival
PB	Peripheral blood
PMF	Primary myelofibrosis
PV	Polycythemia vera
S/A/R	SRSF2/ASXL1/RUNX1
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated hematologic neoplasm
SM-no-AHN	Systemic mastocytosis not associated with a hematologic neoplasm
SSM	Smoldering systemic mastocytosis
VAF	Variant Allele Frequency
WBC	White blood cells
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Author contributions

OH and JR conceived the study. WRS coordinated data extraction. OD performed data management and statistical analyses. GD, JL, JS, MH, FS, PP, NN, MN, AG, MM, KS, SDB, FW, NVB, HB, DS, CE, JV, ABF, SE, KB, TMF, JP, DC, CB, ASY, LM, MD, VS, IT, MB, KH, ARü, MSci, VB, IAF, ASt, MT, RP, SKK, MMak, SP, PVD, ID, DB, TG, MJ, OL, MHe, CBL, SB, CG, SDS, OT, LF, MA, AMi, JNW, HCKN, JNGOE, JG, MSpe, ARe, PV, and WRS contributed patients and data to the ECNM registry. OH, OD, and JR drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request, subject to approval by the ECNM registry steering committee and in compliance with applicable ethical and data protection regulations.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board/ethics committee at each participating center in the European Competence Network on Mastocytosis (ECNM) registry. All patients provided written informed consent prior to inclusion in the ECNM registry.

Consent for publication

Not applicable.

Competing interests

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