Characteristics and outcomes associated with CD2 and CD25 expression on bone marrow mast cells in patients with systemic mastocytosis

Mastocytosis corresponds to a heterogeneous group of hematologic disorders characterized by the accumulation of neoplastic mast cells (MC) in one or more organs. The World Health Organization (WHO) and the International Consensus Classification (ICC) described several variants of mastocytosis, including cutaneous mastocytosis (CM), MC sarcoma (MCS), and systemic mastocytosis (SM).[1,2] SM has been subsequently divided into non-advanced SM (including bone marrow [BM] mastocytosis, indolent SM [ISM], and smoldering SM) and advanced SM (Adv-SM). The Adv-SM subgroup includes aggressive SM (ASM), MC leukemia (MCL), and SM with associated hematologic neoplasm (SM-AHN). In the majority of cases, adults with mastocytosis harbor a D816V mutation in the *KIT* tyrosine kinase domain (TKD).[3] Other *KIT* mutations have been described in the juxtamembrane domain, and some patients have wild-type (WT) *KIT*.[4] Furthermore, an abnormal phenotype for CD2, CD25 or CD30 expression on BMMC (as assessed with immunohistochemistry or flow cytometry) is considered to be pathognomonic of atypical MC.[5,6] The WHO and ICC classifications differentiate several morphological patterns, including well-differentiated SM (WDSM), which can occur in any type of SM.[7] WDSM is morphologically characterized by round mast cells with a well-granulated mature appearance, a low prevalence of the *KIT* mutation, and an almost complete lack of expression of CD2 and CD25, whereas CD30 is expressed. Apart from WDSM, few studies have investigated the characteristics and outcomes associated with the expression of CD2 and CD25 in SM. One report found a higher frequency of CD2 expression in SM compared to CM, while another study observed a non-significant trend towards a lower frequency of CD2 expression in Adv-SM compared to ISM.[8,9]

Patients with Adv-SM have a worse prognosis than those with non-Adv-SM, and the main therapeutic goal is to prolong survival. Until recently, cladribine was the standard treatment for patients with Adv-SM. Although the marketing authorization of tyrosine kinase inhibitors (TKI) targeting the D816V-mutated KIT receptor (midostaurin and avapritinib) has significantly prolonged survival times in Adv-SM, allogeneic hematopoietic stem cell transplantation remains the only curative therapy.[10-12] Thus, the identification of prognostic factors for time to treatment failure (TTF) and overall survival (OS) is critical for the optimization of patient care. The Mutation-Adjusted Risk Score for Adv-SM (MARS) has become the reference score in this population.[13] However, the prognostic impact of abnormal phenotypes has not been extensively characterized. The objective of the present study was to investigate the characteristics and outcomes of mastocytosis patients as a function of their BMMC expression of CD2 and CD25.

All diagnoses of mastocytosis were based on the WHO 2016 classification. The study data were collected by medical staff at the French National Referral Center for Mastocytosis (CEREMAST, France). All the patients were participating in a retrospective, cross-sectional study sponsored by the French Association for Research Initiatives on MCs and Mastocytosis (AFIRMM). The study was approved by the local investigational review board (CPP G.H. Pitié-Salpêtrière, Paris, France; reference: 93-00) and was conducted in compliance with the principles of the Declaration of Helsinki.

The study included two cohorts of patients with mastocytosis. The first cohort aimed to investigate the characteristics associated with the expression of CD2 and CD25 on MC (discovery cohort), while the second cohort aimed to study the prognostic significance associated with the expression of CD2 in a nationwide cohort of patients with Adv-SM treated with midostaurin (midostaurin cohort). The "discovery cohort" (N=81) included adult patients referred to a CEREMAST reference center for the diagnosis of mastocytosis. Patients were prospectively enrolled over a 4-year period between January 2008 and December 2011. MCS patients were included in the Adv-SM group for analyses. Fresh BM aspirates were immunophenotyped at diagnosis. The midostaurin cohort (N=111) included adult patients retrospectively enrolled with the diagnosis of Adv-SM, available CD2/CD25 phenotyping data, and the presence of C finding(s). The cladribine cohort (N=17) included patients from the midostaurin cohort, who had been treated by cladribine prior to midostaurin therapy.

Eighty-one consecutive adult patients with a diagnosis of mastocytosis were included in the discovery cohort (*Online Supplementary Table S1*); there were 54 patients with non-Adv-SM (including 54 ISM patients) and 27 patients with Adv-SM (including 15 ASM, 8 SM-AHN, 2 MCL, and 2 MCS). Sixty-six patients (81.5%) had a *KIT* D816 mutation, 2 had a juxtamembrane mutation, and 13 had a WT *KIT* gene. Of the 81 BM samples immunophenotyped, MC were detected in 73 (90.1%). Of the 73 samples with detectable BMMC, the phenotypes were as follows: $CD2^+/CD25^+$ (N=58, 79.5%), $CD2^-/CD25^+$ (N=10, 13.7%), $CD2^-/CD25^-$ (N=5, 6.8%), $CD2^+/CD25^-$ (N=0, 0%). We next investigated the relationship between the phenotype and the *KIT* genotype. All the patients with a *KIT* TKD mutation and an evaluable phenotype

(N=58, 79.4%) expressed CD25. In contrast, only 9 of the 14 patients (64.3%) without a *KIT* TKD mutation were CD25$^+$. Specifically, 3 patients with a WT *KIT* (1 with ISM, 1 with SM-AHN, and 1 with MCL) and 2 patients with a juxtamembrane mutation (1 MCL and 1 MCS) were CD25$^-$ (*Online Supplementary Figure S1A*). One patient with MCL initially displayed a juxtamembrane *KIT* mutation (Dup 501-502) with CD25$^-$ BMMC. However, after masitinib therapy (targeting WT and juxtamembrane *KIT* mutations) and remission, the patient relapsed and showed two different BMMC populations: one CD25$^+$ and the other CD25$^-$ (*Online Supplementary Figure S1B*). This phenotypic mosaicism was confirmed by immunochemistry, and the appearance of CD25 coincided with the detection of a sub-clonal *KIT* D816 mutation. Sorting of CD25$^+$ BMMC confirmed that the *KIT* D816H mutation was restricted to this compartment and was absent from the CD25$^-$ population.

Expression of CD2 on BMMC was significantly more frequent in non-Adv-SM patients (45/50, 90%) than in Adv-SM patients (13/23, 57%, *P*=0.003) (*Online Supplementary Table S1*). To specifically investigate the association between a lack of CD2 expression on BMMC and the characteristics and outcomes of patients with Adv-SM, we retrospectively constituted a cohort of 111 midostaurin-treated patients, of whom 53 (47.7%) were CD2$^-$ (Table 1). CD2$^-$ patients were more likely to be male (81%, *vs.* 64% of CD2$^+$ patients, *P*=0.042) and to present with a low platelet count (114 *vs.* 148x10^9/L, respectively, *P*=0.016), have adverse additional mutations (i.e., *SRSF2 / ASXL1 / RUNX1*; 61%, *vs.* 39%, respectively, *P*=0.048), and were more likely to die (72%, *vs.* 36%, respectively, *P*<0.001). Accordingly, the median OS time was significantly lower in midostaurin-treated CD2$^-$

Table 1. Characteristics of the patients with advanced systemic mastocytosis, according to their expression of CD2 on bone marrow mast cells.

Variable	CD2 expression			
	Overall N=111[1]	Negative N=53[1]	Positive N=58[1]	*P*
Age in years	68 (60-76)	70 (65-76)	68 (59-74)	0.3[2]
Male sex	80 (72)	43 (81)	37 (64)	0.042[3]
WHO classification ASM MCL SM-AHN	 27 (24) 9 (8) 75 (68)	 10 (37) 3 (33) 40 (53)	 17 (63) 6 (67) 35 (47)	0.3[4] - - -
AHN subtypes CMML MDS MPN MDS/MPNu	 34 (45) 23 (31) 6 (8.0) 12 (16)	 17 (50) 15 (65) 2 (33) 6 (50)	 17 (50) 8 (35) 4 (67) 6 (50)	0.5[4] - - - -
AML transformation	21 (28)	13 (62)	8 (38)	0.4[3]
AHN progression	20 (28)	14 (70)	6 (30)	0.13[3]
Allo-HSCT	14 (13)	7 (50)	7 (50)	0.9[3]
Hepatomegaly	72 (71)	33 (46)	39 (54)	0.6[3]
Splenomegaly	85 (83)	42 (49)	43 (51)	>0.9[3]
Adenopathy	59 (65)	26 (44)	33 (56)	0.3[3]
Cutaneous mastocytosis	52 (53)	20 (39)	32 (61)	0.059[3]
Portal hypertension - ascites	40 (38)	22 (55)	18 (45)	0.3[3]
Malabsorption, weight loss	67 (64)	38 (57)	29 (43)	0.035[3]
Osteolytic lesions	29 (28)	15 (52)	14 (48)	0.7[3]
Response to midostaurin	60 (58)	31 (52)	29 (48)	0.4[3]
Causes of midostaurin discontinuation allo-HSCT Relapse/refractory Intolerance	 4 (5) 60 (74) 17 (21)	 2 (50) 35 (58) 5 (29)	 2 (50) 25 (42) 12 (71)	0.10[4] - - -
Hemoglobin, g/dL	10.10 (9.12-11.90)	9.95 (8.60-11.70)	10.25 (9.30-12.35)	0.3[2]
Leukocytes, x10^9/L	8 (4-13)	8 (5-13)	7 (4-11)	0.3[2]

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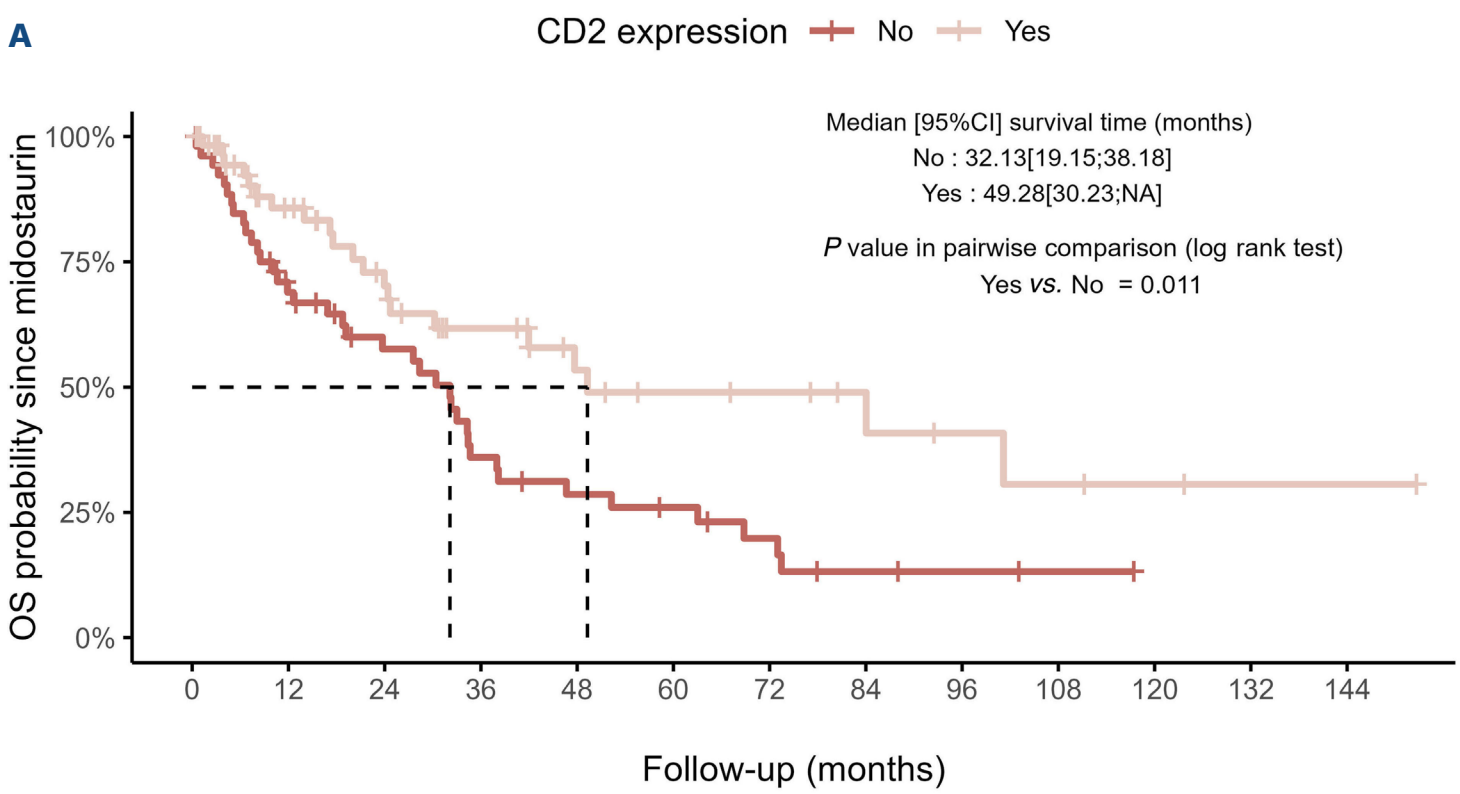
Variable	CD2 expression			
	Overall N=111[1]	Negative N=53[1]	Positive N=58[1]	*P*
Neutrophils, x10^9/L	4.2 (2.0-7.2)	5.7 (2.2-8.7)	4.0 (1.9-6.2)	0.2[2]
Eosinophils, x10^9/L	0.35 (0.06-1.29)	0.33 (0.07-1.01)	0.37 (0.06-1.84)	0.5[2]
Monocytes, x10^9/L	1.00 (0.46-1.81)	1.00 (0.37-1.89)	0.83 (0.50-1.54)	0.7[2]
Basophils, x10^9/L	0.00 (0.00-0.02)	0.00 (0.00-0.00)	0.00 (0.00-0.03)	0.4[2]
Lymphocytes, x10^9/L	1.22 (0.80-1.90)	1.21 (0.76-1.85)	1.27 (0.94-1.90)	0.4[2]
Platelets, x10^9/L	126 (78-172)	114 (73-140)	148 (91-196)	0.016[2]
Albumin level, g/L	35.7 (30.9-40.2)	35.7 (31.9-39.7)	36.5 (30.8-41.0)	0.5[2]
Tryptase level ≥200 ng/mL	47 (43)	20 (43)	27 (57)	0.3[3]
Alkaline phosphatase level > ULN	48 (67)	24 (50)	24 (50)	0.7[3]
KIT mutation				0.3[4]
D816V	100 (92)	46 (46)	54 (54)	-
D816X	3 (3)	2 (67)	1 (33)	-
Wild-type	5 (5)	4 (80)	1 (10)	-
Abnormal karyotype	10 (15)	6 (60)	4 (40)	0.7[4]
SRSF2/ASXL1/RUNX1				0.048[3]
No *S/A/R* mutations	42 (51)	14 (33)	28 (67)	
>1 *S/A/R* mutations	40 (49)	22 (55)	18 (45)	
CD25	107 (99)	52 (49)	55 (51)	>0.9[4]
MARS category				0.15[3]
Low-risk	28 (31)	9 (32)	19 (68)	-
Intermediate-risk	20 (22)	9 (45)	11 (55)	-
High-risk	43 (47)	24 (56)	19 (44)	-
ISPM category				>0.9[4]
Low-risk	8 (11)	4 (50)	4 (50)	-
Intermediate-risk 1	27 (38)	14 (52)	13 (48)	-
Intermediate-risk 2	37 (51)	19 (51)	18 (49)	-
Time since diagnosis in months	26 (10-48)	27 (12-45)	24 (9-50)	0.9[2]
Time since start of midostaurin in months	20 (8-42)	19 (8-38)	21 (7-42)	0.9[2]
Deaths	59 (53)	38 (64)	21 (36)	<0.001[3]

WHO: World Health Organization; ASM: aggressive systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm; MCL: mast cell leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; MDS/MPNu: myelodysplastic syndrome / myeloproliferative neoplasm unclassified; AML: acute myeloid leukemia; allo-HSCT: allogeneic hematopoietic stem cell transplantation; MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis; IPSM: International Prognostic Scoring System; ULN: upper limit of normal. IPSM score includes: age >60 years, tryptase concentration >125 ng/mL, leukocytes >16x10^9/L, hemoglobin <11 g/dL, platelets <100x10^9/L and skin involvement.[16] Response to midostaurin defined according to Valent criteria per physician discretion based on clinical and biological parameters. All *KIT* sequencing in the midostaurin cohort performed by nested PCR[17] or by droplet digital PCR. D816X corresponds to two D816Y and one D816H mutations. [1]Median (IQR); N (%). [2]Wilcoxon's test. [3]Pearson's χ^2 test. [4]Fisher's exact test. Data were quoted as the median (interquartile range [IQR]) for continuous variables and the frequency (%) for categorical variables. Groups were compared in a non-parametric Wilcoxon test for continuous variables and in a χ^2 or Fisher's exact test (as appropriate) for categorial variables. *P*<0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.3.0).

Adv-SM patients than in midostaurin-treated CD2$^+$ Adv-SM patients (32.1 *vs.* 49.3 months, respectively, *P*=0.011) (Figure 1A). Next, we assessed the prognostic impact of CD2 expression on patients having received cladribine. We identified 17 patients (including 11 CD2$^-$ patients) in the midostaurin cohort who had been treated with cladribine prior to the initiation of midostaurin. The median TTF was significantly lower in CD2$^-$ patients than in CD2$^+$ patients (3.4 *vs.* 7.0 months, respectively, *P*=0.043) (Figure 1B). Lastly, we studied the prognostic impact of CD2 expression on OS in a multivariable analysis with the other MARS laboratory parameters (*Online Supplementary Table S2*). In a univariable analysis, WHO classification, platelet count, hemoglobin level, *SRSF2 / ASXL1 / RUNX1* mutations, and CD2 expression were associated with poor OS. However, in a multivariable analysis, only the platelet count was still associated with poor OS (Hazard Ratio=0.99, *P*=0.005).

Our study provides valuable diagnostic and prognostic information. All patients with a non-TKD genotype lacked CD25 expression on their BMMC. Therefore, the absence of these immunophenotypic and molecular criteria (i.e., TKD mutation) may prompt physicians to screen for other *KIT*



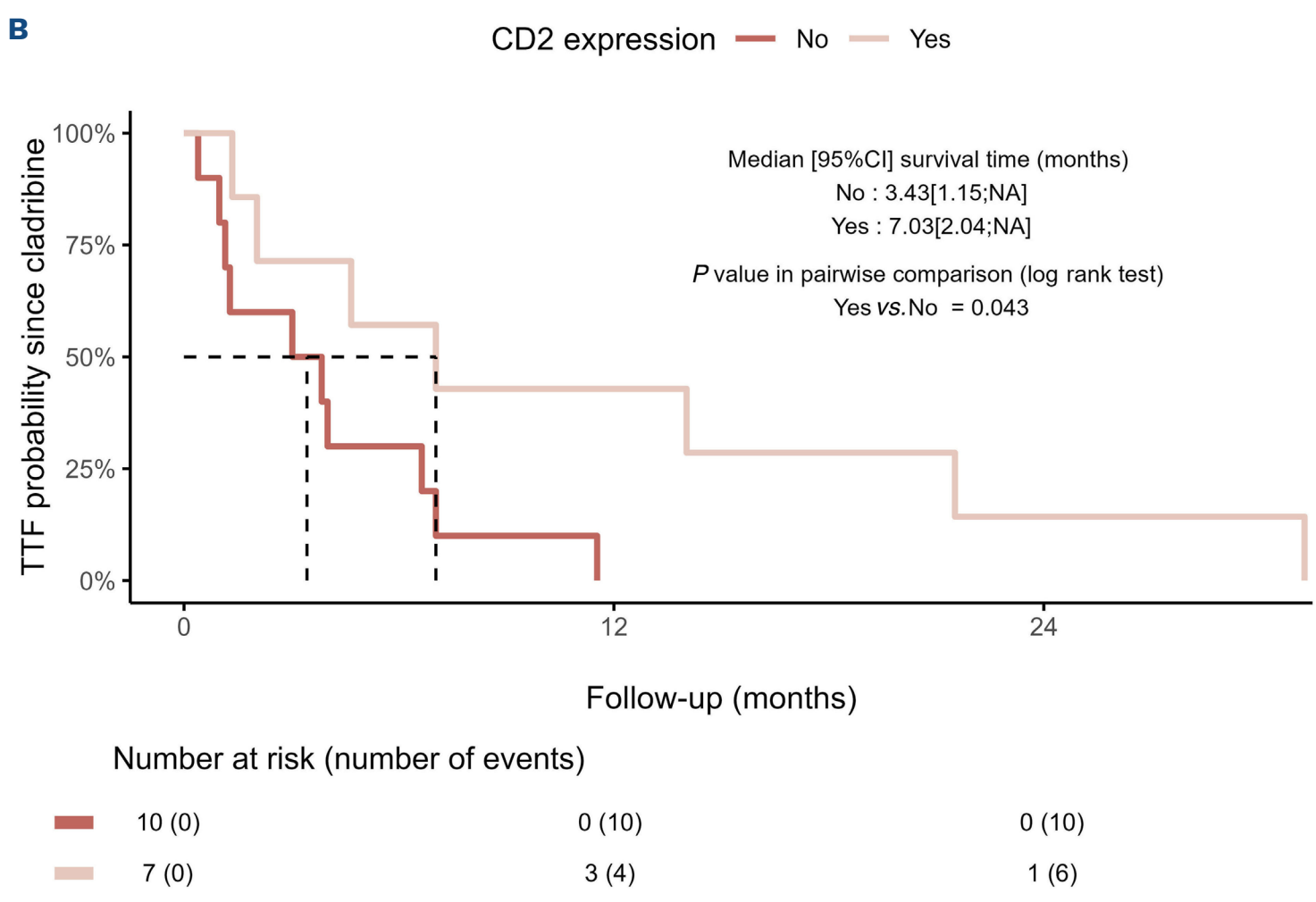


Figure 1. Outcomes of advanced systemic mastocytosis patients treated with midostaurin or cladribine according to CD2 expression on mast cells. (A) Kaplan-Meier estimates of overall survival (OS) according to CD2 expression on bone marrow (BM) mast cells in midostaurin-treated patients with advanced systemic mastocytosis (Adv-SM). (B) Kaplan-Meier estimates of time to treatment failure (TTF) according to CD2 expression on BM mast cells in cladribine-treated patients with Adv-SM. OS and TTF since the start of treatment for each group were analyzed using the Kaplan-Meier estimator. Estimates of hazard functions were compared using the log rank test. CI: Confidence Interval; NA: not achieved.

mutations. In this context, based on the MC morphology and the expression of CD30 on MC, a WDSM should be considered. In addition, we confirmed a previous report regarding the association between the absence of CD2 expression in Adv-SM compared with ISM patients. This observation could be explained by the previous study reporting that the lack of CD2 may be associated with the loss of CD2-CD58 interaction.[14] This could lead to the absence of homotypic aggregation, resulting in the spreading of SM into extramedullary organs. We also provided further findings on the association between the lack of CD2 expression on BMMC, adverse additional mutations, and poor outcomes. In addition to the potential increased risk of spreading of $CD2^-$ tumoral MC, this finding might be explained by lower platelet levels and a tendency towards a higher frequency of *KIT* D816V-negative status among $CD2^-$ patients, who have been associated with a poor prognosis.[15] Besides the potential interest from a pathophysiological perspective, the poor prognostic significance of the lack of CD2 may serve as a cost-effective tool for identifying high-risk Adv-SM patients, especially when next-generation sequencing (and thus the MARS score) is not available. Further studies are required to determine whether this prognostic impact is present in patients treated with avapritinib.

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Contributions

JR, SGL, OH, GD and LL are responsible for study conception and design. LL, CB, OB and VA are responsible for immunophenotypic analysis. DC is responsible for histopathology and immunohistochemistry. JR, SGL, DC, PD, OH, VA, GD and LL are responsible for data collection and analysis. JR, SGL, GD, OH and LL take principal responsibility for writing the manuscript. All authors gave their final approval of the manuscript for publication.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. Hemasphere. 2021;5(11):e646.
2. Wang SA, Orazi A, Gotlib J, et al. The international consensus classification of eosinophilic disorders and systemic mastocytosis. Am J Hematol. 2023;98(8):1286-1306.
3. Arock M, Hoermann G, Sotlar K, et al. Clinical impact and proposed application of molecular markers, genetic variants, and cytogenetic analysis in mast cell neoplasms: Status 2022. J Allergy Clin Immunol. 2022;149(6):1855-1865.
4. Yang Y, Létard S, Borge L, et al. Pediatric mastocytosis-associated KIT extracellular domain mutations exhibit different functional and signaling properties compared with KIT-phosphotransferase domain mutations. Blood. 2010;116(7):1114-1123.
5. Sánchez-Muñoz L, Morgado JM, Álvarez-Twose I, et al. Diagnosis and classification of mastocytosis in non-specialized versus reference centres: a Spanish Network on Mastocytosis (REMA) study on 122 patients. Br J Haematol. 2016;172(1):56-63.
6. Escribano L, Díaz-Agustín B, Bellas C, et al. Utility of flow cytometric analysis of mast cells in the diagnosis and classification of adult mastocytosis. Leuk Res. 2001;25(7):563-570.
7. Álvarez-Twose I, Jara-Acevedo M, Morgado JM, et al. Clinical, immunophenotypic, and molecular characteristics of well-differentiated systemic mastocytosis. J Allergy Clin Immunol. 2016;137(1):168-178.
8. Morgado JMT, Sánchez-Muñoz L, Teodósio CG, et al. Immunophenotyping in systemic mastocytosis diagnosis: 'CD25 positive' alone is more informative than the 'CD25 and/or CD2' WHO criterion. Mod Pathol. 2012;25(4):516-521.
9. Lange M, yawrocki A, Nedoszytko B, et al. Does the aberrant expression of CD2 and CD25 by skin mast cells truly correlate with systemic involvement in patients presenting with mastocytosis in the skin? Int Arch Allergy Immunol. 2014;165(2):104-110.
10. Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021;27(12):2192-2199.
11. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med. 2016;374(26):2530-2541.
12. Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol. 2014;32(29):3264-3274.
13. Jawhar M, Schwaab J, Álvarez-Twose I, et al. MARS: mutation-adjusted risk score for advanced systemic mastocytosis. J Clin Oncol. 2019;37(31):2846-2856.
14. Schernthaner G-H, Jordan J-H, Ghannadan M, et al. Expression, epitope analysis, and functional role of the LFA-2 antigen detectable on neoplastic mast cells. Blood. 2001;98(13):3784-3792.
15. Naumann N, Rudelius M, Lübke J, et al. Poor applicability of currently available prognostic scoring systems for prediction of outcome in KIT D816V-negative advanced systemic mastocytosis. Cancers (Basel). 2024;16(3):593.
16. Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol. 2019;6(12):e638-e649.
17. Polivka L, Madrange M, Bulai-Livideanu C, et al. Pathophysiologic implications of elevated prevalence of hereditary alpha-tryptasemia in all mastocytosis subtypes. JACI. 2024;153(1):349-353.e4.