International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 08, Issue 10, October 2023,
https://doi.org/10.23958/ijirms/vol08-i10/1762

Original article

Clinical Characteristics of Patients with Aggressive Systemic Mastocytosis and Efficacy Analysis of Systemic Therapies: A Monocentric Real-World Experience

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Received 21 September 2023; Accepted 28 September 2023; Published 06 October 2023

Abstract

Introduction and Objective: Aggressive systemic mastocytosis is a lethal disease with poor prognosis in which organ damage due to mast cell activation is observed and response to medical treatment is low. The aim of this study was to evaluate the clinicopathological characteristics of ASM patients and the efficacy of cytoreductive treatments. ***Patients and methods:*** The clinicopathological features and survival analyses of 27 patients who were followed up with a diagnosis of aggressive systemic mastocytosis (ASM) and treated with cytoreductive therapy between 2017 and 2021 in our center were evaluated. ***Results:*** The mean age of the patients was 59 years and there was a slight male gender predominance (5: 4). KITD816V mutation was positive in 85% of cases. The most common symptoms at the time of diagnosis were fatigue, pruritus and dyspeptic complaints, respectively. The number of patients evaluable for response to imatinib, peginterferon alfa-2a (Peg-Ifn), cladribine and midostaurin treatments were 4, 7, 8 and 8, and the overall (partial) response rates were 25% (25%), 42% (28%), 50% (38%) and 37% (25%), respectively. Most of the responses were partial (PR) and major response (MR) was seen in very few patients. Increasing ECOG score, serum tryptase level, spleen size, and WBC count increased mortality, while decreasing hemoglobin level increased mortality. General median overall survival (OS) was 27.74 months (35.11-143.88). Two-year survival rate was 88.9% and 5-year survival rate was 63.1%. Median overall disease-free survival (DFS) was 10.86 months (9.27-12.50). Two-year DFS was 22.2%, while 5-year DFS was only 7.4%. ***Conclusion:*** The depth of response and response rates of the current therapies used in the treatment of ASM are quite low and insufficient to control the disease. Since there is an unmet therapeutic area in the treatment of ASM, there is a need for the development of new treatment modalities.

Keywords: ***aggressive systemic mastocytosis, cytoreductive therapy, survival.***

Introduction

Aggressive systemic mastocytosis (ASM) is a lethal disease with poor prognosis, usually resistant to treatment, in which organ damage is seen due to excessive proliferation of mast cells in various organs and excessive secretion of vasoactive mediators [1]. Mastocytosis according to the World Health Organisation (WHO) 2022 classification is divided into three as cutaneous, systemic and mast cell sarcoma. Among these, systemic mastocytosis is divided into six as bone marrow mastocytosis(BMM), indolent SM (ISM), smoldering SM (SSM), clonal non-mast cell hematological disease lineage disease (SM-AHNMD), ASM and mast cell leukemia(MCL) [2]. The presence of tryptase and/or CD117 positive multifocal dense infiltrates with 15 or more mast cells in tryptase and/or CD117 positive multifocal dense infiltrates detected in tissue biopsy sections in bone marrow or other organs other than skin is the main criterion for the diagnosis of SM [3]. High serum tryptase level (>20 ng/mL) and presence of KIT D816V mutation are minor diagnostic criteria. KIT D816V mutation is found in more than 90% of SM cases [4]. In patients who meet the diagnostic criteria for SM, ASM is diagnosed in the presence of cytopenia, liver dysfunction and C findings such as ascites, palpable hepatomegaly, bone lesions, palpable splenomegaly and hypoalbuminemia accompanying malabsorption [5]. Itching, diarrhea, skin rashes, nausea, vomiting, abdominal pain and gastrointestinal bleeding are common symptoms of the disease [6]. Serum tryptase levels are increased in SM [7].

In ASM, anti-mediator therapy is given to alleviate symptoms, but often symptomatic improvement is not seen without cytoreductive therapy [8]. The aim of cytoreductive therapy is to control symptoms by reducing mast cell load and activity, to stop the progression of the disease and to prolong survival by preventing the development of organ damage [9]. There is no curative treatment option other than allogeneic stem cell transplantation for patients with ASM. Since allogeneic stem cell transplantation (Allo-HSCT)

is only recommended in young and selected patients, Allo-HSCT is considered an experimental treatment in advanced ASM [10]. Imatinib mesylate, cladribine, midostaurin and interferon alpha are available therapeutic options in ASM [11]. These therapeutic options are not curable, and treatment aims to control symptoms and disease progression.

The aim of this study was to evaluate the clinicopathological characteristics of ASM patients and the efficacy of cytoreductive treatments.

Material and method

This study is a retrospective single-center observational study. The study started in January 2017. The data cut-off date for the current analysis was January 2021. In the hematology clinic of Çukurova University Faculty of Medicine, 27 patients diagnosed with ASM according to the WHO 2016 classification [12] were retrospectively analysed. All of the patients had at least one of the c findings such as bone marrow dysfunction, liver dysfunction, ascites, palpable hepatomegaly, bone lesions, palpable splenomegaly and hypoalbuminemia accompanying malabsorption All patient taken and assessed a bone marrow aspirate and a bone marrow biopsy to exclude SM-AHN. Informed consent was obtained from all patients for sharing their diagnostic and treatment-related data. Patients' data were accessed both from medical records and electronically. Patients who did not provide informed consent (according to local regulations) or whose medical records were not available were not eligible for included in the study.

As first line cytoreductive therapy, imatinib (400 mg orally daily) (patients without the KIT D816V mutation), peginterferon alfa-2a (Peg-Ifn) (90 µg subcutaneously once a week), midostaurin (100 mg orally twice daily) and cladribine (0.14 mg/kg subcutaneously for 5 days) were administered until progression. "IWG-MRT-ECNM consensus criteria" were used to evaluate the response to treatment (**Table 1**) [13]. The results of the treatments and survival analyses were reviewed.

Table 1: IWG-MRT-ECNM consensus criteria for patients with ASM, MCL, and SM associated with a myeloid neoplasm [13].

Complete remission (CR)*
Requires all 4 criteria and response duration must be ≥ 12 wk
No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ
Serum tryptase level < 20 ng/mL†
Peripheral blood count remission defined as ANC ≥ 1 × 10^9/L with normal differential, Hb level ≥ 11 g/dL, and platelet count ≥ 100 × 10^9/L
Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (CI findings)‡
Partial remission (PR)*
Requires all 3 criteria and response duration must be ≥ 12 wk, in the absence of both CR and progressive disease (PD)
Reduction by ≥ 50% in neoplastic MCs in the marrow and/or or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage
Reduction of serum tryptase level by ≥ 50%†
Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (CI finding(s)) ‡
Clinical improvement (CI)*
Response duration must be ≥ 12 wk
Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled (see Table 3) in the absence of both CR/PR assignment or progressive disease (PD)
Stable disease (SD)
Not meeting criteria for CR, PR, CI, or PD
Progressive disease (PD)§
Requires at least 1 element of either criteria 1 or 2 and duration must be ≥ 8 wk
(1) For patients with baseline grade 2 nonhematologic organ damage: a) worsening by 1 grade, AND b) minimum 100% increase (doubling) of laboratory abnormality.
For patients with baseline ≥ grade 2 albumin: (a) worsening by 1 grade, AND (b) decrease by ≥ 0.5 g/dL.
For patients with baseline ≥ grade 3 nonhematologic organ damage: minimum 100% increase (doubling) of laboratory abnormality.
For patients with baseline ≥ grade 2 transfusion-independent anemia or thrombocytopenia: New transfusion dependence of ≥ 4 units of RBCs or platelets at 8 wk.
For patients with baseline transfusion-dependent anemia or thrombocytopenia: ≥100% increase in the average transfusion frequency for an 8-wk period compared with the 12-wk pretreatment period
For patients with baseline grade ≥ grade 3 neutropenia: (a) > 50% decrease in neutrophil count, AND (b) absolute decrease of neutrophil count of ≥ 250/mm^3, AND c) grade 4
(2) Development of at least 10-cm palpable symptomatic splenomegaly for a baseline spleen size of not palpable or ≤ 5 cm, OR if baseline symptomatic splenomegaly is > 5 cm, a > 50% worsening and development of at least 10 cm of palpable symptomatic splenomegaly compared with the baseline value.¶
Loss of response (LOR)
Loss of a documented CR, PR, or CI that must be for ≥8 wk. Downgrading of CR to PR or PR to CI is considered as such but is not considered as loss of response unless CI is also lost for a minimum of 8 wk. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.

Guidelines for adjudicating response are as follows: (1) Only disease-related ≥ grade 2 organ damage is evaluable as a primary endpoint in clinical trials. (2) Response adjudications of CR, PR, SD, PD, and LOR should only be applied to these ≥ grade 2 organ damage findings in the context of trials. (3) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ grade 2 organ damage finding(s). (4) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ grade 2 organ damage.

*Responses that are not maintained or confirmed for a period of at least 12 wk do not fulfill criteria for CR, PR, or CI; however, both maintained and unmaintained (< 12-wk duration) responses in organ damage should be recorded to determine median duration of response.

†Only valid as a response criterion if the pretreatment serum tryptase level is ≥ 40 ng/mL.

‡Biopsy of organ(s) in addition to the BM to evaluate for SM-related organ damage may be considered.

§Preservation of at least one CI finding permits a patient to maintain the response of 'CI' if 1 or more CI findings are lost but none meet criteria for progressive disease (PD). However, if 1 or more of the CI findings become PD, then the CI finding assignment is lost and the patient meets criteria for PD. The baseline value for evaluating PD is the pretreatment measurement(s). The PD findings must be considered related to the underlying disease and not to other clinical factors. Progression of an underlying chronic myeloid neoplasm to AML is also considered PD in the setting of clinical trials.

¶For clinical trials using 3D computed tomography or magnetic resonance imaging as an additional modality to quantify organomegaly, progression in splenomegaly is defined as an increase in spleen volume of at least 25%.

The study protocol was approved by the Ethics Committee of Çukurova University Faculty of Medicine under the decision no. 76, dated 6 January, 2023. In addition, the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines issued by the International Conference on Harmonisation.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables and Mean±SD or Median (IQR)

for continuous variables. When the data of the study were analysed in terms of normality assumptions, Independent t test, one of the parametric tests, and Mann Whitney U test, one of the non-parametric tests, were used to determine whether there was a significant difference between mortality and various clinical variables and laboratory values. Fisher's Exact test was used to compare categorical variables. Finally, Univariete and Multivariete Cox Regression results of various clinical factors on mortality risk and disease-free survival risk are given. $p<0.05$ was considered statistically significant.

Results

Among 27 patients diagnosed with ASM with ECOG scores of 1 (60%) and 2 (40%), 12 (44%) were female and 15 (56%) were male with a mean age of 59 years. One third of the patients had comorbidity. KITD816V mutation, which is a minor diagnostic criterion, was present in 85% of the patients. Demographic, laboratory and radiological data of the patients are given in Table 2 and the median follow-up period was 46. 7 months.

Table 2: Distribution of Sociodemographic and Clinical Information of Patients

		n (%)
Demographic variables		
Gender	Female Male	12 (44.4) 15 (55.6)
ECOG score	1 2	16 (59.3) 11 (40.7)
Comorbidity	None Present	18 (66.7) 9 (33.3)
KITD816V Mutation (Real-Time qPCR)	None Present	4 (14.8) 23 (85.2)
	Mean±SD	Median (min-max)
Age (years)	59±9	60(41-78)
BM-MC (%)	17.7±2.2	17(15-19.9)
Triptase (mg/L)	192.9±117.1	130(54-380)
Spleen Size (cm)	14.4±3.3	13(10-22)
WBC (10^3/ul)	14937±5764.4	12900(7700-26000)
Hemoglobin (g/dL)	10.7±1.7	11(7.9-14)
LDH (U/L)	347.8±142.8	300 (148-697)
Follow-up Period (months)	36.7±28.9	36.8 (13.17-135.6)

BM-MC (%), bone marrow mast cell percentage; WBC, white blood cell; LDH, lactate dehydrogenase

The symptoms seen in the patients at the time of diagnosis are shown in Table 3 in order of frequency. The most common symptom at the time of diagnosis was fatigue (70%). Itching (59%), dyspeptic complaints (48%), abdominal pain (44%), pain in the bones (40%), diarrhea (40%), musculoskeletal- articular pain (22%) and neuropsychiatric complaints (14%) were the most common symptoms after fatigue (**Table 3**).

Table 3: Symptoms at Diagnosis

	n (%)
Fatigue	19(70.3)
Itching	16(59.2)
Dyspeptic complaints	13(48.1)
Abdominal Pain	12(44,4)
Pain in the Bones	11(40.7)
Diarrhea	11(40.7)
Muscle and Joint Pain	6(22.2)
Neuropsychiatric complaints	4(14.8)

The number of patients who could be evaluated in terms of response to imatinib, Peg-Ifn, cladribine and midostaurin treatments applied for cytoreductive purposes in ASM treatment were 4, 7, 8 and 8 and the overall (partial) response rates were 25% (25%), 42% (28%), 50% (38%) and 37% (25%), respectively. Most of the responses were at the PR level and the CR rate was very low (**Table 4**). The most favorable responses were observed in the patient group receiving cladribine. The medications were generally well tolerated. One patient receiving imatinib had grade 4 peripheral edema and two patients receiving midostaurin were discontinued due to nausea and vomiting refractory to antiemetic treatment. No side effects requiring medication discontinuation were observed in patients receiving Peg-Ifn and cladribine.

Table 4: Response Status to Cytoreductive Therapies

First Line Treatment and Number of Patients	**ORR**	**CR n (%)**	**PR n (%)**	**MFD (month)**
Imatinib (n:4)	25	0(0)	1(25)	25
Peg-Ifn (n:7)	42	1(14)	2(28)	38
Cladribin (n:8)	50	1(12)	3(38)	41
Midostaurin (n:8)	37	1(12)	2(25)	32

CR, complete response; ORR, overall response rate; PR, partial response; MFD, mean follow-up duration.

As seen in Table 5, ECOG score (p=0.015), serum tryptase (p=0.004), BM MC% (p=0.001), spleen size (p=0.002), WBC (p=0.001), hemoglobin (p<0.001), and LDH (p=0.001) levels showed a statistically significant difference between ex and survivors. ECOG score, tryptase, BM MC%, spleen size, WBC and LDH levels were found to be higher in those who died compared to those who survived. However, hemoglobin level was found to be lower in those who died compared to those who survived.

Table 5: Correlation of Various Clinical and Laboratory Parameters with Mortality

	Survivor n=16	Ex n=11	p
ECOG score, n (%)			
1	13 (81.3)	3 (27.3)	0.015a
2	3 (18.7)	8 (72.7)	
Triptase (mg/L), Median (IQR)	98.5(89.7)	326(215)	0.004[b]
BM-MC (%), Median (IQR)	16(3.6)	18(4)	0.001[b]
Spleen size (cm), Median (IQR)	12(2.75)	17(5)	0.002[b]
WBC (10^3/ul), Median (IQR)	10150(3500)	19900(7500)	0.001[b]
Hemoglobin (g/dL), Mean±SD	11.61±1.35	9.39±1.30	<0.001[c]
LDH(U/L), Median (IQR)	275.00 (51.50)	379.00 (300)	0.001[b]

WBC, white blood cell; LDH, lactate dehydrogenase

a: Fisher's Exact test; b: Mann Whitney U test; c: Paried samples t test, p<0.05 is statistically significant

Table 6: Survival data of all patients

Months	Median (%95 CI)
OS (months)	27.7 (35.1-143.9)
PFS (months)	10.9 (9.3-12.5)

Kaplan Meier curve, Long rank test, p<0.05 is statistically significant

As shown in Table 6, the overall median OS was 27.7 (35.11-143.88) months. Two-year survival rate was 88.9% and 5-year survival rate was 63.1%. Median disease-free survival (DFS) was 10.9 (9.27-12.50) months. Two-year disease-free survival rate was 22.2% and 5-year disease-free survival rate was only 7.4%.

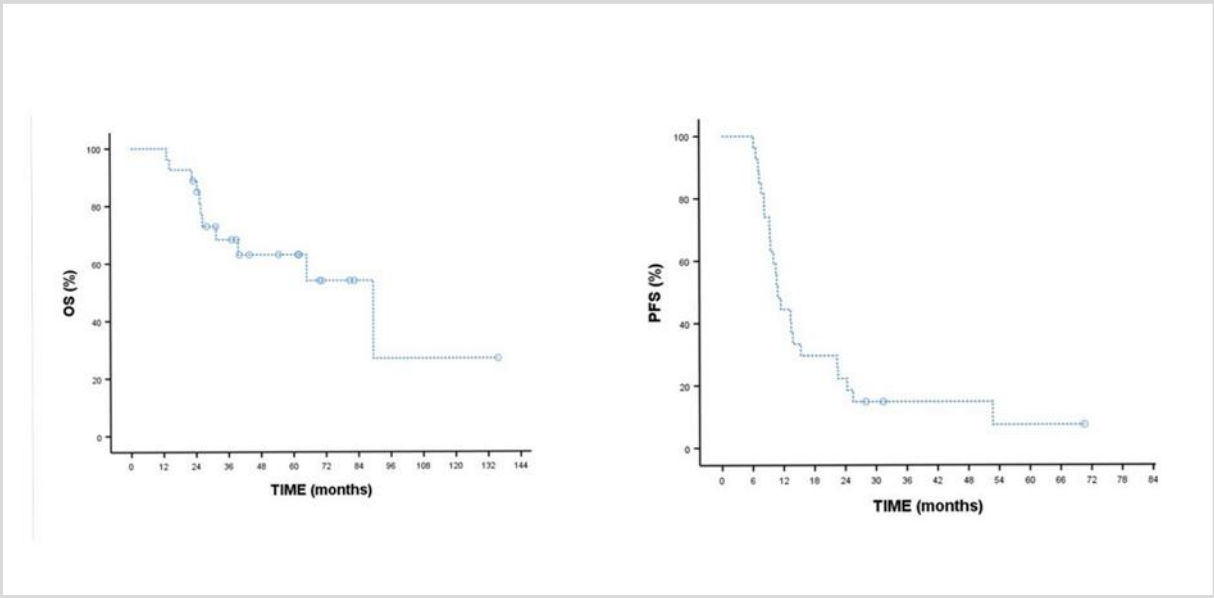

Figure 1: OS and PFS of patients with ASM

Discussion

Mastocytosis is an aggressive and rare disease in which organ dysfunction is seen due to the release of vasoactive mediators from clonal mast cells that abnormally accumulate and activate in various organs [14]. Antimediator therapy aims to inhibit the bioactive mediators produced by MCs secreted in excess by mast cells. For many years, antimediator therapy agents such as histamine receptor antagonists, glucocorticosteroids, cromolyn sodium and immunotherapy were used alone for the treatment of SM. Antimediator therapy is recommended to control symptoms in all mastocytosis subtypes [15]. The addition of cytoreductive therapy to antimediator therapy varies depending on the clinical findings and the subtype of the disease. In ISM and SSM, where the rate of progression is relatively low, only antimediator therapy is initially recommended. In ASM, cytoreductive therapy is recommended to prevent life-threatening mast cell proliferation since the rate of progression is quite high and survival is quite low [16].

Symptoms are very effective in making treatment decision in SM patients [17]. Skin lesions, rash, diarrhea, abdominal pain, neuropsychiatric or musculoskeletal complaints are frequently observed in systemic mastocytosis [18,19]. Anemia of chronic disease, iron deficiency, gastrointestinal bleeding and anemia due to renal failure are commonly found in SM. Fatigue secondary to anemia is one of the most common symptoms. In our patient population, the most common symptom was fatigue and the least common symptom was neuropsychiatric complaints (**Table 3**).

Since ASM is a rare disease, the available evidence for the treatment of the disease comes from the few clinical trials and observational studies reported in the literature. Since real-world data are scarce in rare diseases such as ASM, the reported results are very important in defining the efficacy and safety of treatments. The standard of care for the management of the disease remains unclear. Off-label cytoreductive therapies such as midostaurin and imatinib and off-label cytoreductive therapies such as interferon alpha and cladribine, which are widely used in ASM patients, aim to reduce mast cell burden and control the disease. In this study, unlike other studies, we applied peginterferon alfa-2a treatment instead of interferon alfa because it is better tolerated and provides ease of use. To the best of our knowledge, this study is the first report in the literature presenting the efficacy of imatinib, midostaurin, cladribine and peginterferon alfa-2a treatments in ASM as a real life experience.

In patients with both KIT D816V and wild-type KIT mutations, midostaurin, which inhibits multiple receptor tyrosine kinases, has proven to be effective on mastocytosis-related organ damage. Based on data from this phase 2 study, midostaurin received FDA approval for the treatment of ASM in 2017 [20]. Gotlib et al. found an overall response rate (ORR) of 60% to midostaurin treatment in 89 patients with ASM. A major response, defined as complete resolution of at least one type of organ damage associated with mastocytosis, occurred in 45% of patients. In this study, median OS was 28.7 months and median progression-free survival was 14.1 months. Serum tryptase levels and bone marrow mast cell burden decreased by at least 50% in most patients after midostaurin treatment. In a recent study comparing the efficacy of midostaurin and cladribine in 139 patients with ASM, patients (n = 139) were treated with midostaurin alone (n = 63, 45%), cladribine alone (n = 23, 17%) and other patients sequentially (midostaurin-cladribine, n = 30, 57%; cladribine-midostaurin). In monotherapy, midostaurin was superior to cladribine and provided a significantly improved OS (median 4.2 versus 1.9 years, P = 0.033) and leukemia-free survival (2.7 versus 1.3 years, P = 0.044) [21].

Another tyrosine kinase inhibitor, imatinib mesylate, received FDA approval in 2006 in adult ASM patients with unknown or unknown D816V KIT mutation due to the favorable effects shown in ASM cases and case series. In a phase 2 open-label study, 11 of 14 ASM patients responded to imatinib 400 mg daily. Bone marrow mast cell counts decreased in 8 of 13 patients with evaluable response, skin symptoms resolved in 5 of 9 patients, hepatosplenomegaly improved in 3 of 6 patients, and symptoms resolved in 8 of 13 patients. Imatinib mesylate was found to be effective in SM, including those with the D816V mutation [22].

Cladribine is a synthetic purine analogue medicine that inhibits adenosine deaminase [23]. Cladribine is used for cytoreductive treatment in ASM due to its apoptotic and proliferation-stopping effect on neoplastic mast cells [24]. Barete et al. detected ASM in 14 of 68 mastocytosis patients in a long (>10 years) follow-up study. In these 14 patients treated with cladribine, ORR was reported as 43% and MR rate as 36% [25].

In chronic myeloproliferative disorders, peginterferon alfa-2a is the most commonly used form of interferon because of its ease of weekly administration and because it is the agent with the most experience. Once it was recognised that patients with mastocytosis can develop myeloproliferative disease, the use of IFN therapy began to increase [26]. IFN therapy reduces pro-inflammatory cytokines in mastocytosis, reduces mast cell proliferation and degranulation, and improves end organ damage caused by mast cells [27]. Interferon alpha-2b (IFN-a) has been used for cytoreductive therapy in the treatment of SM for more than 30 years [28]. In a study of 80 SM patients with evaluable response (ISM and ASM 60%; SM-AHNMD 45%), half of these patients received IFNa and the ORR was 53% The overall median duration of response (DOR) was 12 months (range 1-67 months) [29].

KIT D816V mutation is detected in the majority of SM cases. Avapritinib, which provides potent and specific inhibition in KIT D816V mutant patients, was approved in adults with ASM in June 2021. The approval was based on the multicenter, single-branch, open-label Phase 1 EXPLORER study. In 53 patients with evaluable response included in the study, the ORR was 75% and the CR rate was 36%. Avapritinib reduced bone marrow mast cell burden in 92% of patients and serum tryptase by ≥50% in 99%. Avapritinib was shown to induce deep and durable responses and was well tolerated at the recommended phase 2 dose of 200 mg daily [30]. Furthermore, in Phase II PATHFINDER, the primary endpoint was successfully fulfilled with an ORR of 75% (95% confidence interval 57-89) in 32 ASM patients with evaluable response (P=1.6×10^9) [31]. Reductions in serum basal tryptase ≥50% (93%), bone marrow mast cells (88%) and D816V variant allele fraction (60%) were observed. The Phase II PATHFINDER study confirmed the efficacy and safety of avapritinib shown in the Phase 1 EXPLORER study.

Lim et al. performed cytoreductive therapy in 108 adults with SM. Twenty-seven patients received a median starting dose of 400 mg imatinib mesylate daily. In 22 patients with evaluable response, ORR with imatinib treatment was 18% (ORR in ISM, ASM and SM-AHNMD was 14%, 50% and 9%, respectively) and DOR was 19.6 months (range 9-69 months). Among these, interferon-alpha was administered to 47 patients, and treatment response was evaluable in 40 patients, with an ORR of 53% (ORR in ISM, ASM and SM-AHNMD were 60%, 60% and 45%, respectively). Twenty-six (26) patients were also treated with cladribine. Treatment response was evaluable in 22 patients and the ORR was 55% (ORR in ISM, ASM and SM-AHNMD was 56%, 50% and 55%, respectively). DOR was 11 months (range 3-74 months). Although major response rates after cytoreductive therapy were suboptimal in this study, cladribine or IFN-α is recommended as the current first-line treatment in SM [32].

In a study involving 1639 patients diagnosed with mastocytosis, ASM was detected in 259 of the patients. In the total cohort, median overall survival was 28.4 years (95% CI 19.5-37.0) and 10-year overall survival was 81.9% (95% CI 7.7-84.7). OS and PFS were significantly different between patients without advanced mastocytosis and patients with advanced mastocytosis (p<0.0001). The prognosis was worse in the ASM cohort with a median OS of 5.7 years (95% CI 0.6-4.5). Mastocytosis Prognostic Scoring System (IPSM) scores are used to predict survival outcomes and guide treatment decisions in patients with mastocytosis. According to IPSM, parameters associated with poor prognosis such as advanced age (>60), anemia, thrombocytopenia, leukocytosis and tryptase elevation were more frequent in the ASM variant. The prognostic value of the WHO classification was confirmed in this study [33]. In our study, ECOG score, tryptase, bone marrow mast cell burden, spleen size, leukocytosis, low hemoglobin and elevated LDH were found to be significantly higher in ex patients (p<0.05).

In a study presented at the recent European Hematology Association 2022 (EHA 2022) congress, 176 patients treated with avapritinib, 94 treated with midostaurin (LOT, n=99) and 44 treated with cladribine (LOT, n=49) were included in a study comparing therapies used in the treatment of ASM and providing real-life data [34]. In the avapritinib cohort, median follow-up was 17.9 months and median OS was not reached (NR) (95% CI: 46.9, not estimable). In the midostaurin cohort, median follow-up was 27.9 months and

median OS was 28.6 months (95% CI: 18.2, 44.6). For the cladribine cohort, the median follow-up was 24.2 months, during which 29 (66%) patients deceased. The median OS in the cladribine cohort was 23.4 months (95% CI: 14.8, 40.6). The authors reported that avapritinib was associated with significantly better survival in real life compared to midostaurin or cladribine.

What constitutes standard of care in primary care in ASM remains unclear today. There is an ongoing demand for targeted therapies with a favorable side-effect profile. We used peginterferon alfa-2a, which is generally well tolerated in chronic myeloproliferative disorders.

In real-life data, the mean follow-up time of ASM treatment modalities is usually shorter than three years. The best response rate reported so far has been reported in patients receiving avapritinib, with most responses at the PR level. In our study, the best response rates were seen in patients receiving cladribine and Peg-Ifn, with most responses remaining at the PR level. Medication intolerance in patients receiving midostaurin may have decreased the response rates of this agent in ASM.

Author Contributions

İ.H.A. designed and performed the experiments and wrote and revised the manuscript; B.G. provided materials, designed and analyzed the data, and wrote and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study protocol was approved by the Institutional Review Board (IRB) of Çukurova University Faculty of Medicine under the decision no 76, dated 6 January, 2023. Written informed consent was waived in light of the urgent need to collect and report data.

Informed Consent Statement

Written informed consent was waived in light of the urgent need to collect and report the data.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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