Mediterranean Journal of Hematology and Infectious Diseases

Review Article

Treatment of Indolent and Advanced Systemic Mastocytosis

Alessandro Buonomo[1], Eleonora Nucera[1] and Marianna Criscuolo[2].

[1] Allergy Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
[2] Department of Radiological and Hematological Sciences Fondazione, Policlinico Universitario A. Gemelli, IRCCS Università Cattolica del Sacro Cuore, Largo A. Gemelli, 100168, Rome, Italy.

Competing interests: The authors declare no conflict of Interest.

Abstract. Management of Indolent and Smoldering SM is focused on preventing anaphylactic reactions and identifying and avoiding symptom triggers. Skin and gastrointestinal symptoms are managed with H1- and H2-antihistamines. When skin symptoms are not adequately controlled, leukotriene antagonists and oral psoralen combined with ultraviolet therapy may be added. Proton pump inhibitors, sodium cromolyn, and oral corticosteroids may be added for gastrointestinal symptoms. Patients should be prescribed self-injectable epinephrine and trained to treat recurrent cardiovascular symptoms or anaphylaxis. Depression and cognitive impairment require a psychiatric evaluation for tailored treatment. Bone involvement is managed with bisphosphonates and eventually interferon. Omalizumab is effective on all vasomotor symptoms, including anaphylaxis, but not on respiratory, musculoskeletal, and neuropsychiatric symptoms. A cytoreductive treatment is not recommended unless anti-mediator therapy has failed. Venom immunotherapy is mandatory for patients with Hymenoptera venom allergy.
There is no curative option for patients with advanced SM. The available therapeutic options include tyrosine-kinase inhibitors and cladribine, with variable duration and extent of response. Imatinib mesylate was the first drug approved for SM lacking the cKIT D816V mutation; dasatinib and nilotinib are ineffective. Midostaurin is active on both wild-type and mutant cKIT D816V, while Avapritinib is a selective cKIT D816V inhibitor: they are approved for the treatment of advanced SM. Cladribine is a purine analog with significant activity against monocytes that were thought to have a common progenitor with mast cells. Allogeneic stem cell transplantation is usually performed in younger selected patients.

Keywords: Macrocytosis; Therapy.

Citation: Buonomo A., Nucera E., Criscuolo M. Treatment of indolent and advanced systemic mastocytosis. Mediterr J Hematol Infect Dis 2022, 14(1): e2022040, DOI: http://dx.doi.org/10.4084/MJHID.2022.040

Published: May 1, 2022 **Received: March 2, 2022** **Accepted: April 14, 2022**

Correspondence to: Marianna Criscuolo. E-mail: marianna.criscuolo@policlinicogemelli.it

Introduction. Systemic mastocytosis (SM) is a myeloproliferative neoplasm resulting from a clonal expansion of morphologically and immunophenotypically abnormal mast cells (MCs). A gain-of-function somatic mutation in the *KIT* gene, which codifies for a tyrosine kinase, is responsible for uncontrolled MC proliferation and survival.[1] MCs are effector cells of an immune response, especially involved in parasites infections control and allergic and anaphylactic reactions.

Mastocytosis is characterized by protean clinical manifestations: the release of several mediators and cytokines is responsible for symptoms that involve skin, gastrointestinal tract, cardiovascular system, bone, and neurological and psychological status.

Table 1. Treatment of Indolent and Smoldering SM.

Symptoms	First Choice	Second Choice	Third Choice	Fourth Choice
Skin	first and second generation **H1-antihistamines** escalated up to 4 times their recommended dose	**leukotriene antagonists** montelukast 10 mg, zafirlukast 20 mg bid	oral **psoralen** with ultraviolet therapy	
Gastrointestinal	**H2-antihistamines** ranitidine 150 mg bid, famotidine 10 mg bid, cimetidine 400 mg bid	**proton pump inhibitors** omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg	**sodium cromolyn** 800-1200 mg daily divided in 4 doses	oral **corticosteroids** prednisone 0.5-1 mg/kg/day or equivalent
Cardiovascular	self-injectable **epinephrine**, antihistamines, Omalizumab, hospital admission			
Neurologic	psychiatric evaluation			
Osteoporosis	**bisphosphonates** Os alendronate 70 mg a week, risedronate 35 mg a week; IV pamidronate 90 mg a month zoledronate 5 mg every 12-18 months or 4 mg a month in more severe conditions	**interferon α** 1-3 MU 3 times per week up to 3-5 MU 3-5 times per week **denosumab** 60 mg subcutaneously every 6 months		**cladribine** 5 mg/m2 per 5 days every 4-8 weeks
Recurrent Anaphylaxis		**Omalizumab,** dosage not defined (150 to 300 mg subcutaneously every 2 weeks to every four week)		
Hymenoptera venom allergy	**venom immunotherapy**	**Omalizumab,** dosage not defined (150 to 300 mg subcutaneously every 2 weeks to every four week)		

Treatment of Indolent SM and Smoldering SM. Management of Indolent SM (ISM) and Smoldering SM (SSM) is focused on the prevention and treatment of anaphylactic reactions and symptom control (**Table 1**). In case of severe symptoms refractory to anti-mediator therapy or bone disease unresponsive to bisphosphonates, disease-modifying treatments with cytoreductive agents may be attempted.

The first approach is to identify symptom triggers and suggest avoidance strategies of triggers, such as physical stimuli (heat, change of temperature, pressure, cold, rubbing), exercise, sleep deprivation, emotions, drugs (opiates, contrast media, succinylcholine, nonsteroidal anti-inflammatory drugs, agents with tetrahydroisoquinoline such as quinolones, atracurium, and rocuronium), alcohol, food, and Hymenoptera stings.[2,3]

Skin. Flushing, urticaria (wheals), itching, angioedema, and dermatographism are the most frequently reported skin symptoms in ISM and SSM. H1-antihistamines are the first-line drugs in this setting: first-generation sedating molecules (diphenhydramine, hydroxyzine, ketotifen, doxepin, cyproheptadine) and second-generation non-sedating molecules (cetirizine, levocetirizine, loratadine, desloratadine, ebastine, rupatadine, bilastine, mozolastine) are available. First-generation antihistamines should be used at bedtime, especially when cutaneous symptoms impair sleeping quality. Dosage of antihistamines (especially second-generation molecules) may be escalated up to 4 times their recommended dose for chronic spontaneous urticaria, with no relevant side effects. A recent review shows that antihistamines can improve patients' quality of life, reduce wheals and itching on standardized provocation testing, and improve symptoms like itching, flushing, tachycardia, and headache.[4]

When H1-antihistamines do not adequately control skin symptoms, leukotriene antagonists (montelukast 10 mg, zafirlukast 20 mg bid) may be added. Unfortunately, Zileuton, a 5-lipoxygenase inhibitor, is not available in Europe.

Aspirin can be used as a third-line treatment for skin symptoms, starting from 81 mg bid to 500 mg bid if nonsteroidal anti-inflammatory drugs are tolerated. Its effect should be monitored by measuring prostaglandine2 metabolite excretion. On the other hand, aspirin use may increase cysteinyl leukotrienes, causing/worsening vasoconstriction and bronchospasm.[5]

Finally, oral psoralen combined with ultraviolet therapy is reserved for patients with cutaneous mastocytosis (urticarial pigmentosa) in case of severe/resistant skin symptoms.[6,7]

Gastrointestinal tract. Abdominal pain, cramping, nausea, vomiting, heartburn, gastroesophageal reflux, and diarrhea may be present in both ISM and SSM. H2-antagonists (ranitidine 150 mg bid, famotidine 10 mg bid, cimetidine 400 mg bid) are the drug of choice in case of gastrointestinal symptoms.[1,3] They inhibit gastric acid secretion via the H2-receptors and, associated with H1-antihistamines, reduce the release of mediators from MCs,[8] but they are less effective in controlling diarrhea.[9]

Proton pump inhibitors (omeprazole 20 mg,

pantoprazole 40 mg, rabeprazole 20 mg) are second line drugs in case H2-antihistamines are not effective.[1,3]

Sodium cromolyn at a dose of 800-1200 mg daily divided into four doses is a third-line treatment. It acts as a stabilizing agent on MC membranes and reduces MC degranulation by interfering with Ca^{++} influx. In addition, sodium cromolyn has shown to be effective in the management of gastrointestinal symptoms when compared to placebo.[10]

Oral corticosteroids (prednisone 0.5-1 mg/kg/day or equivalent) are the fourth-line drug for gastrointestinal symptoms. However, because of their side effects, corticosteroids should be tapered as soon as possible based on the patient response.[1,6]

Cardiovascular symptoms. SM patients may have recurrent presyncope or syncope, hypotension, tachycardia, or anaphylaxis. The prevalence of anaphylaxis in adults with SM ranges from 22 to 49%, about 100 times higher than the general population. Anaphylaxis may be provoked by a concomitant IgE-mediated allergy (especially to Hymenoptera venoms) or may also be spontaneous. Thus, all patients should be prescribed self-injectable epinephrine and should be trained to treat attacks.[2,11]

Acute episodes of anaphylaxis should be treated according to current guidelines. The drug of choice is intramuscular epinephrine at a dosage of 0.3-0.5 mg, followed by fluid replacement (saline or Ringer lactate), 500-1000 mg of intravenous hydrocortisone and intravenous H1 H2-antihistamines.[12] Prevention of new episodes is based on chronic treatment with H1- and H2-antihistamines and leukotriene antagonists, while oral corticosteroids (prednisone 0.5-1 mg/kg/day) should be proposed only in very resistant patients.[1,3] Recently, a relevant role has been reported for Omalizumab to resolve cardiovascular symptoms with or without anaphylaxis.[13] When this approach is ineffective, a cytoreductive therapy with cladribine or interferon α (IFN α) can be taken into consideration.[3]

Neurologic symptoms. Depression, headache, cognitive impairment, and sleep disturbance are common. H1-antihistamines showed to be effective on headaches but not on other symptoms. Therefore, these patients should undergo a psychiatric evaluation for a prompt start of tailored treatment.[4]

Osteoporosis. Bone involvement leading to osteopenia, osteoporosis, and fragility fractures are frequent in SM patients: the reported prevalence ranges from 18 to 31%. It is important to note that an osteoporotic fracture is not considered a sign of aggressive disease, as opposed to the rarely encountered large, osteolytic bone lesions that can sometimes be detected in patients with ASM or MCL and are classified as a C-finding. The pathogenesis of osteoporosis has been attributed to the cytokines and other mediators released from mast cells. Tumor necrosis factor (TNF)-α, interleukin(IL)-1, and IL-6 promote osteoclast activity and inhibit osteoblasts. Moreover, histamine has a stimulatory effect on osteoclasts and their precursors.[14]

Since there is a relative or absolute prevalence of bone reabsorption, bisphosphonates are the first-line treatment option. Several molecules are available orally (alendronate 70 mg a week, risedronate 35 mg a week) and intravenously administered (pamidronate 90 mg a month; zoledronate 5 mg every day 12-18 months or 4 mg a month in more severe conditions). They positively affect vertebral bone mineral density (BMD) and less on femoral neck BMD. Zoledronate showed the best positive effect on both vertebral and femoral neck BMD.[15]

In case of very severe osteoporosis and/or onset of new major fractures, the use of IFN-α should be considered. IFN-α is able to decrease MC burden and MC-related symptoms but may be poorly tolerated for flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism, leading to poor compliance.[1]

It is administered subcutaneously from a starting dose of 1-3 million units (MU) three times per week to 3-5 MU 3-5 times per week.

Finally, when bisphosphonates and IFN-α fail, a cytoreductive treatment with the purine nucleoside analog 2-chlorodosxyadenosine (cladribine/2CdA) at a dosage of 5 mg/m^2 per 5 days every 4-8 weeks is the third-line treatment. Immunosuppression and myelosuppression are important side effects that may lead to drug discontinuation.[16]

Denosumab, a monoclonal antibody directed against RANK-ligand(L), has been developed to treat postmenopausal osteoporosis. RANKL, which is expressed by MCs, can activate osteoclast by the RANK pathway. Denosumab, at the dosage of 60 mg subcutaneously every six months, showed to be effective in increasing BMD at both vertebral and femoral neck sites after one year of treatment. Denosumab could be used as a second-line in patients not responding to bisphosphonates or not candidates to bisphosphonates because of renal insufficiency: further studies in larger samples are necessary to assess efficacy.[17]

Omalizumab. Omalizumab, an anti-IgE humanized monoclonal antibody, is approved to treat chronic spontaneous urticaria and extrinsic bronchial asthma when standard treatments are not effective at maximum doses. At present, the optimal dose and frequency of administration remain to be determined (150 to 300 mg subcutaneously every two weeks to every four weeks).

The largest trial included 55 patients with a mast cell disorder that received Omalizumab. The diagnoses were

ISM (29 patients), MC activation syndrome (MCAS), and Cutaneous Mastocytosis (CM). A *KIT* D816V mutation was found in 27 of 49 patients (particularly those with ISM). The recommended starting dose was 150 mg subcutaneously every two weeks. Omalizumab response was rapid, with a median time to first response of 2 months and the best response after six months. It was effective on all vasomotor symptoms, including those secondary to anaphylaxis, and gastrointestinal and urinary symptoms, with a good safety profile.[18]

In a smaller trial including 14 patients, the authors showed a significant improvement of vasomotor symptoms and quality of life. However, the treatment was less effective for gastrointestinal, musculoskeletal, and neuropsychiatric symptoms.[19] In addition, the Schedule of drug administration (starting and maintenance doses) varied among patients, considering initial symptoms, clinical response, and treatment tolerance.

A recent review showed that omalizumab treatment led to a complete resolution of anaphylaxis episodes in 84% of the patients, while the efficacy on respiratory, musculoskeletal, and neuropsychiatric symptoms was scarce. The authors concluded that a randomized controlled trial is mandatory to demonstrate the usefulness of Omalizumab in SM treatment.[13]

Cytoreductive Treatment of ISM and SSM. A cytoreductive treatment is not recommended for ISM and SSM unless anti-mediator therapy has failed.[20]

Midostaurin is a multikinase inhibitor that is able to inhibit the kinase activity of both wild-type and D816V mutated *KIT*. An open-label, non-randomized phase 2 trial was conducted on 20 patients with ISM and severe mediator symptoms not controlled with standard therapy. After 12 weeks, patients showed a significant reduction in symptom-score and improved quality of life. In addition, tryptase levels showed a significant decrease. All patients stopped midostaurin after 24 weeks, and most of them showed a relapse. Nausea, headache, and diarrhea were the most common side effects. The effect on anaphylaxis-like symptoms was not studied because of the insufficient number of subjects with cardiovascular symptoms.[21]

Masitinib, an oral tyrosine kinase inhibitor, was used in a randomized, double-blind, placebo-controlled phase 3 trial. One hundred thirty-five adults patients with ISM and SSM were enrolled in the study: 71 received masitinib and 64 placebo. The dosage was 6 mg/kg per day in two doses. The primary endpoint was the cumulative response in at least 1 of 4 severe baseline symptoms (itching, flushing, depression, asthenia). After 24 weeks, masitinib showed a significant cumulative response in the primary endpoint compared to placebo (18.7% vs. 7.4%). The most frequent adverse events in the active group were diarrhea, rash, and asthenia.[22]

Avapritinib (BLU-285), a multikinase inhibitor, is a second-generation inhibitor of *KIT* D816V. In a randomized, double-blind, placebo-controlled phase 2 trial (NCT03731260), avapritinib significantly improved mediator symptoms compared to placebo, with a good safety profile. The dosage ranged from 25 to 100 mg in a daily administration.

Cladribine is a synthetic purine analog that inhibits DNA repair, blocks dividing cells, and induces apoptosis in resting cells. It is effective in reducing must cell burden in ASM and SM-AHN patients. Thirty-six subjects with IM (6 CM, 28 ISM, and 2 SSM) were included in the study. Each course of treatment was repeated with a 4 to 12-week interval for a maximum of 9 courses at a dosage of 0.14 mg/kg/day from 1 to 5 days. The treatment showed a significant improvement in flushing, itching, neuropsychiatric and cardiovascular symptoms with a concomitant reduction of tryptase levels. Common side-effects were myelosuppression-related toxicity (47%) and infectious complications (22%).[16]

Hymenoptera Venom Allergy and Mast Cell Activation Syndromes. There is a frequent association between severe Hymenoptera venom allergy (HVA) and elevated basal serum levels (>11.4 ng/mL). For example, some authors found that 9 out of 137 (6.6%) patients with severe drug or food allergy (6.6%) had a basal tryptase >11.4 ng/mL, and only two (1.5%) were diagnosed with mastocytosis. On the other hand, 13.9% of patients with HVA had elevated tryptase, and 11.1% had a clonal mast cell disorder.[23]

American authors found a mastocytosis prevalence of 10.1 per 100000 overall and 96.7 per 100000 among HVA patients. Nine out of 161 (5.6%) patients undergoing venom immunotherapy (VIT) had basal tryptase >11.4 ng/mL, and 3 (1.8%) had a clonal mast cell disorder.[24]

Typically, HVA in mastocytosis patients is characterized by the absence of urticaria/angioedema and the sudden onset of cardiovascular symptoms leading to loss of consciousness. For this reason, these patients should carry with them an emergency kit including two epinephrine autoinjectors and should be trained in their use by the allergist.[23]

VIT is mandatory since it is the only life-saving treatment for these patients, and it should be prolonged long-life with a 3-4 month-interval, according to European and American guidelines.[25] Mastocytosis patients are at higher risk of reactions during build-up and maintenance phases, but some authors recently observed no adverse events in 8 patients undergoing 12 ultra-rush VIT, both in the build-up and maintenance phases. Nevertheless, because of severe reactions, expert personnel should carry out an ultra-rush protocol with the prompt availability of resuscitation equipment.[26,27] In

addition, some patients may experience recurrent anaphylaxis following Hymenoptera sting and/or extremely invalidating intolerance to VIT. In these cases, Omalizumab has been reported to induce tolerance to VIT and reduce anaphylaxis episodes[13] successfully.

Treatment of Advanced Systemic Mastocytosis. The term advanced systemic mastocytosis (advSM) identifies three different diseases, namely aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). These subtypes are characterized by mast cell-related organ damage, for which a cytoreductive treatment is usually required, and a reduced survival.[1]

Considering the protean clinical manifestations, the evaluation of aggressiveness involves different body systems such as bone marrow, liver, spleen, bones, and gastrointestinal tract, globally classified as C findings. On the other hand, constitutional symptoms may be more invalidating in some patients than the organ damage itself. The complexity of the disease has led to the development of several response evaluation criteria during the last 20 years, updated to include the grading resolution of C findings and constitutional symptoms.[28-31]

Until now, there is no curative option for patients with AdvSM. The available therapeutic options include tyrosine-kinase inhibitors, interferonα, and cladribine, with variable duration and extent of response (**Table 2**). Allogeneic stem cell transplantation is usually performed in younger selected patients.

Imatinib Mesylate. Imatinib mesylate is an in vitro inhibitor of several tyrosine kinases, particularly wild-type and specific mutant ckit.[32,33] It was the first drug specifically approved by the FDA for adult patients with SM lacking the cKIT D816V mutation or unknown cKIT mutational status at 400 mg daily dosage. This indication came after a report by Pardanani et al.,[34] in which 12 adults with symptomatic SM were treated with imatinib mesylate 100 mg up to 400 mg daily. Three patients with eosinophilia (1 with ISS and 2 with ASM, all cKIT D816V negative) obtained a complete remission, and 2 ASM patients without eosinophilia obtained a bone marrow cytoreduction and improvement of bone pain. However, three patients with ASM were refractory to imatinib mesylate, irrespective of blood eosinophil count; 2 patients with prevalent skin involvement had a progressive decrease of symptoms, and two were not evaluable for response.

A Dutch open-label phase II study reported on the efficacy of imatinib mesylate among 14 patients, mostly with non-advSM.[35] The authors found a reduction of hepatosplenomegaly and skin/constitutional symptoms in almost half of the study population, more pronounced in cKIT D816V negative but also detectable in cKIT D816V positive patients. However, the concomitant use of steroids may have contributed to the response.

Another American prospective open-label phase II study recruited 11 patients with ISM and nine patients with AdvSM for treatment with imatinib mesylate at 400 mg daily.[36] During a median time on therapy of 9 months, 1 AdvSM patient and 6 ISM patients reported improvement of symptoms; nevertheless, all patients interrupted the treatment for loss of response. The authors concluded that imatinib mesylate might only produce a significant clinical benefit in patients without cKIT D816V mutation.

A monocentric retrospective study published in 2009 reported the outcome of 27 patients with ISM (30%) and AdvSM (70%) treated with imatinib mesylate at a starting dose of 400 mg daily.[37] Among 22 evaluable patients, only four responded (18% overall): 1 ISM patient, 2 ASM patients, and 1 SM-AHN patient; the median duration of response was 19.6 months for all patients (range 9-69 months).

More recently, in 2017, a phase IV clinical trial tested the response to imatinib mesylate of 10 patients with CM

Table 2. Treatment of Advanced SM.

Drugs	Class	Dosage	Efficacy
Imatinib mesylate	tyrosine kinase inhibitor, specific cKIT mutation	100 mg up to 400 mg daily	bone marrow burden, constitutional symptoms
Interferon α	cytokine	3.5-30 MU weekly	skin involvement, osteoporosis, constitutional symptoms
Cladribine	purine nucleoside analogue	0.13-0.17 mg/kg or 5 mg/mq 5 days a week repeated with a minimum interval of 4 weeks (n° of cycles not defined)	bone marrow burden, constitutional symptoms, skin involvement
Midostaurin	tyrosine kinase inhibitor, both wild type and mutant cKIT	100 mg twice daily	C findings, bone marrow burden, constitutional symptoms
Avapritinib	tyrosine kinase inhibitor, selective for cKIT	200 mg once-daily	C findings, bone marrow burden, constitutional symptoms
Allogeneic stem cell transplantation	chemotherapy	myeloablative conditioning and peripheral blood source	Anecdotal (recommended in selected cases)

and SM with cKIT mutation found outside the activation loop-coding region or wild-type cKIT.[38] Four patients obtained a complete response in terms of MC burden in the bone marrow, normalization of tryptase level, and resolution of constitutional symptoms; 1 patient obtained a partial response involving both MC burden and symptoms. All five unresponsive patients were wild-type cKIT. The authors concluded that imatinib mesylate is effective among SM patients with specific cKIT mutational status (i.e., mutation involving the extracellular and transmembrane regions) while is less effective than previously reported in true wild type cKIT.

Interferon α. Historically, interferonα was the first treatment of SM, used by analogy with other myeloproliferative neoplasms,[39-41] sometimes in combination with steroids.

A prospective multicentre phase II trial reported only 35% partial response and 30% minor response among 13/20 evaluable patients with ISM and ASM.[42] In this study, interferon α 3MU/m2 thrice weekly for six months improved both skin involvement and constitutional symptoms while ineffective in organ involvement. However, the authors also reported a discrete rate of withdrawal, mainly because of worsening of cytopenia, and the reappearance of systemic symptoms soon after the interruption of the drug, even for patients who previously responded.

An Austrian study enrolled five patients treated with interferonα and steroids.[43] The authors reported two complete resolutions of C findings, one partial improvement of C findings, one stable disease, and one progression to MCL.

A monocentric retrospective study published in 2009 reported the outcome of 47 patients with ISM (23%) and AdvSM (77%) treated with interferonα at a median dosage of 15 MU weekly (range 3.5-30 MU weekly).[37] Among 40 evaluable patients, the overall response rate was 53% for all categories, particularly 6 ISM patients, 6 ASM patients, and 9 SM-AHN patients; the median duration of response was 12 months for all patients (range 1-67 months).

The main adverse events of treatment were fatigue, cytopenia, depression, flu-like symptoms, and fever. In most cases, symptoms are easily managed with dose reduction, but some cases of drug interruption for severe cytopenia and/or depression were reported.[42,43]

Cladribine. 2-chlorodeoxyadenosine (2-CdA) is a purine nucleoside analog used in different diseases of hematopoietic origin, with significant activity against monocytes[44] that were thought to have a common progenitor with mast cells.[45]

A cases series of AdvSM patients refractory or intolerant to interferonα reported the outcome of 4 patients after 4-6 cycles of 2-CdA (0.14 mg/kg 5 days a week) given every 1 to 6 months.[46] The authors reported a significant improvement of systemic symptoms and skin rash in three cases and persistence of response long after treatment. In another series of 10 patients with ISM and AdvSM treated with six courses of 2-CdA (0.13 mg/kg 5 days a week), the authors concluded that three patients with ASM obtained a response after a median time of 6 months.[47] Moreover, skin involvement was reduced at least 50% in all affected patients, and bone marrow involvement was significantly reduced in 8 cases; constitutional symptoms were markedly decreased.

A monocentric retrospective study published in 2009 reported the outcome of 26 patients with ISM (38%) and AdvSM (62%) treated with 2-CdA (0.14 mg/kg 5 days a week) given every 1 to 3 months.[37] Among 22 evaluable patients, the overall response rate was 55% for all categories: five ISM patients, one ASM patient, and six SM-AHN patients; the median duration of response was 11 months for all patients (range 3-74 months).

A multicenter French study recruited 68 patients with CM (9%), ISM (44%) and AdvSM (47%) treated with a median of 3 courses (range 1-9) of 2-CdA (0.13-0.17 mg/kg or 5 mg/mq 5 days a week) given every 1 to 3 months.[16] The authors reported an overall response rate of 72%, with the highest response rate in cutaneous/indolent form (100% and 89%, respectively) compared to ASM and SM-AHN (43% and 59%, respectively). Although no complete response was reported, the median duration of response was 3.7 years, with no significant difference between ISM and AdvSM.

The main adverse events of treatment were grade 3-4 myelosuppression and infection, which may lead to dose reduction and treatment delay. Herpes reactivation can be managed with antiviral prophylaxis.[16,47]

Dasatinib. Dasatinib is a tyrosine kinase inhibitor that exerts a potent action on the mutant D816V cKIT in vitro. On this basis, Verstovsek et al. conducted an open-label phase 2 study on 18 ISM and 15 AdvSM patients treated with dasatinib 140 mg daily.[48] The authors reported an overall response rate of 33%: only two patients obtained a complete response, lasting for 5 and 16 months, and both were negative for D816V cKIT mutation; the other nine patients achieved an improvement in constitutional symptoms. The authors concluded that dasatinib is ineffective in treating patients with SM carrying D816V cKIT mutation.

Nilotinib. Nilotinib is a tyrosine kinase inhibitor that is also active against the KIT in vitro. Following preliminary results, Hochhaus et al. conducted a multicenter phase-2 registration trial on 61 patients with advSM (69%) and ISM (31%) treated with nilotinib 400 mg twice a day.[49] Unfortunately, evaluable responses were available only in the ASM group: the authors reported a minor response in 8/37 patients, while no

complete response was documented.

Midostaurin. Midostaurin is a potent multi-target tyrosine kinase inhibitor, active on wild-type and mutant cKIT D816V. Following the preliminary efficacy report, an international multicenter single-group open-label phase-2 study recruited 116 patients with AdvSM for treatment with midostaurin 100 mg twice daily.[50] The authors reported an overall response rate of 46% and a median duration of treatment of 11.4 months (range 0.3-51.5). According to WHO categories, the response rates were 75%, 58%, and 50% for patients with ASM, SM-AHN, and MCL. Responses included improved organ function (reduction of bone marrow burden, spleen volume, and normalization of liver enzymes), reduction or interruption of transfusion dependence, improvement of constitutional symptoms and quality of life, and recovery of weight loss. However, the median duration of response was not reached in patients with ASM (95% CI, 24.1 months to not estimated) and with MCL (95% CI, 3.6 months to not estimated), while it was 12.7 months (95% CI, 7.4 to 31.4) in patients with SM-AHN. Similarly, the median overall survival was not reached (95% CI, 28.7 months to not estimated) in patients with ASM, while it was 20.7 months (95% CI, 16.0 to 44.4) and 9.4 months (95% CI, 7.5 to not estimated) in patients with SM-AHN and MCL, respectively. Overall, median progression-free survival was 14.1 months: in ASM patients, it was 28.7 months, 11.0 months higher than SM-AHN, and 11.3 than MCL patients.

Based on this study, in 2017 FDA approved midostaurin for the treatment of AdvSM, regardless of cKIT D816V mutation status.

Another multicenter phase-2 trial reported on the long-term outcome of 26 patients with AdvSM treated with midostaurin 100 mg twice daily for up to 12 cycles and beyond in case of response.[51] During the 12-cycle period, the overall response rate was 69%, with a median time to response of 25.5 days (range 4–56) and a median time to best response of 56 days (range 25–229). Five patients reported only stable disease, and three patients progressed. The best rate of response was reported in patients with SM-AHN (76%) and MCL (67%), rather than ASM (33%). After the 12-cycle period, the overall response rate did not change. Median overall survival was not reached for 3 ASM, while it was 40 months (95% CI, 24.2–55.9) for the 17 SM-AHN patients and 18.5 months (95% CI, 0–62.2) for MCL patients. Overall, the median PFS was 41.0 months (4.4–77.6).

A Polish study reported data on the real-world efficacy of midostaurin on 13 patients with AdvSM.[52] After a median duration of treatment of 9 months (range 1-21), a clinical benefit was detectable in 77% of patients, and half of the patients with measurable organ damage obtained a response. After a median follow-up of 19 months, the authors reported seven patients with ongoing therapy and three patients died of progressive disease.

The main adverse events of treatment were nausea and vomiting, diarrhea, increased transaminase, and cytopenia. Gastrointestinal symptoms usually improve after the first months of treatment. Cytopenia and abnormal liver function can be managed with drug interruption and dose reduction, according to the toxicity grading.[50-52]

Brentuximab Vedotin. Brentuximab vedotin (BV) is a chimeric immunoglobulin G1, specific to human CD30, covalently attached to the microtubule-disrupting agent monomethyl auristatin E (MMAE) used mostly in lymphoproliferative diseases expressing surface CD30. After in vitro study on CD30+ human mast cell lines, a phase 2, open-label study was performed, with the primary objective of evaluating the antitumor activity of BV in patients with CD30-positive non-lymphoid malignancies.[53] Two patients with ISM and two patients with ASM were included and treated with BV at a dosage of 1.8 mg/kg or 2.4 mg/kg every three weeks. The authors reported one major response, one improvement of constitutional symptoms, and two disease progression.

Another phase 2 open-label, single-group was conducted to determine the efficacy and safety of BV 1.8 mg/kg every three weeks among patients with AdvSM, and at least 20% of surface CD30 expression, assessed by flow cytometry.[54] After a median follow-up of 722 days (range 18-1246 days) and a median number of five cycles (range 1-8 cycles), no significant and/or durable response was observed among ten recruited patients, assessed by reduction of tumor burden and constitutional symptoms. The authors concluded that BV has no clinical activity in this setting of patients.

Avapritinib. Avapritinib (BLU-285) is a selective cKIT D816V inhibitor that showed promising results in phase 1 clinical trial.[55] The phase-1 trial enrolled 53 patients with AdvSM for treatment with avapritinib: among 32 evaluable patients, the overall response rate was 76% after a median follow-up of 27.3 months. At this time, the median overall survival has not been reached in this population.

The phase-2 registration trial reported the outcome of 32 patients treated with avapritinib 200 mg daily.[56] The overall response rate was 75%, specifically 100% for ASM, 81% for SM-AHN, and 25% for MCL. The median time to response was two months, and the median time to best response was 5.6 months; at a median follow-up of 10.4 months, all responses persisted, and median overall survival was not reached.

Based on these data, the FDA approved avapritinib for Adv SM treatment in June 2021.

The main adverse events of treatment were periorbital and peripheral edema, fatigue, gastrointestinal symptoms, cytopenia, and cognitive impairment.[55,56]

Allogeneic Transplantation. The role of allogeneic stem cell transplantation is still not defined in the treatment of disease: debulk strategy, the timing of the procedure, choice of best conditioning regimen and donor source, and possible maintenance therapy post-transplant are still matter of debate in the clinical practice.[57,58]

Allogeneic stem cell transplantation has been performed with various outcomes in mast cell disease patients associated with another hematological neoplasm. Some authors reported the disappearance of leukemia-related mast cells clone after allogeneic transplant,[59] while others showed neoplastic mast cell persistence despite complete remission of concomitant hematological neoplasm.[60] Moreover, evidence of the graft-versus-mast-cells effect implies an immunological mechanism underlying the clearance of neoplastic infiltration.[61,62]

Literature data about conditioning regimens and donor sources are scarce. Nakamura et al. reported the outcome of 3 patients with MCL and SM-AHN conditioned with a non-myeloablative regimen (cyclophosphamide and fludarabine).[63] Engraftment was reached in all 3 cases, and no transplant-related mortality was observed, but all patients relapsed despite a transient graft-versus-mast cell effect after immunosuppression withdrawal. More recently, a retrospective multicenter study reported the outcome of 57 patients with AdvSM transplanted in the United States and Europe: the overall response was about 70% for all categories.[57] Considering survival, the OS and PFS differ among the three categories. Particularly, considering ASM, SM-AHN, and MCL, OS at three years was 43%, 74%, and 17%, respectively, while PFS at three years was 43%, 63%, and 17%. Excluding the patients with MCL, which had the worse prognosis, risk factors for reduced survival were diagnosis of ASM and a reduced-intensity conditioning regimen. All three patients who received a transplant from cord blood and HLA-haploidentical relative and all patients with MCL who received RIC died.

As a general recommendation, myeloablative conditioning and peripheral blood source should be considered in younger people with aggressive clinical course.

Conclusions. Mastocytosis is a complex disease for which a multidisciplinary approach is mandatory for a comprehensive evaluation and choice of therapy. In most cases, patients might need a personalized treatment with a specific combination of different drugs, ranging from antihistamines and bisphosphonates to TKI and chemotherapy. In addition, tolerance of treatment, disease symptoms control, and adverse events should be frequently evaluated and carefully balanced in these patients.

References:

1. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol 2021; 96: 508-525. https://doi.org/10.1002/ajh.26118 PMid:33524167
2. Pardanani A. How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage). Blood 2013; 121 3085-3094. https://doi.org/10.1182/blood-2013-01-453183 PMid:23426950
3. Castells M, Butterfield J. Mast cell activation syndrome and mastocytosis: initial treatment options and long-term management. J Allergy Clin Immunol Parct 2019; 7: 1097-1106. https://doi.org/10.1016/j.jaip.2019.02.002 PMid:30961835
4. Nurmatov UB, Rhatigan E, Simons FER, Sheikh A. H1-antihistamines for primary mast cell activation syndromes: a systematic review. Allergy 2015; 70: 1052-1061. https://doi.org/10.1111/all.12672 PMid:26095756
5. Butterfield JH, Singh RJ. Divergent PGD2 and leukotriene C4 metabolite excretion following aspirin therapy: Ten patients with systemic mastocytosis. Prostaglandins Other Lipid Mediat. 2021 Aug;155:106563. doi: 10.1016/j.prostaglandins.2021.106563. Epub 2021 May 21. https://doi.org/10.1016/j.prostaglandins.2021.106563 PMid:34029712
6. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. Br J Haematol 2018; 180: 11-23. https://doi.org/10.1111/bjh.14967 PMid:29048112
7. Mackey S, Pride HB, Tyler WB. Diffuse cutaneous mastocytosis. Treatment with oral psoralen plus UV-A. Arch Dermatol 1996; 132: 1429-1430. https://doi.org/10.1001/archderm.1996.03890360013002 PMid:8961869
8. Kurosawa M, Amano H, Kanbe N, et al. Heterogeneity of mast cells in mastocytosis and inhibitory effect of ketotifen and ranitidine on indolent systemic mastocytosis. J Allergy Clin Immunol 1997; 100: S25-32. https://doi.org/10.1016/S0091-6749(97)70001-0
9. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. Ann Int Med 1979; 90: 769-771. https://doi.org/10.7326/0003-4819-90-5-769 PMid:373561
10. Horan RF, Sheffer AL, Austen KF. Cromlyn sodium in the management of systemic mastocytosis. J Allergy Clin Immunol 1990; 85: 852-855. https://doi.org/10.1016/0091-6749(90)90067-E
11. Schuch A, Brockow K. Mastocytosis and anaphylaxis. Immunol Allergy Clin N Am 2017; 37: 153-164. https://doi.org/10.1016/j.iac.2016.08.017 PMid:27886904
12. Tanno LK, Alvarez-Perea A, Pouessel G. Therapeutic approach of anaphylaxis. Curr Opin Allergy Clin Immunol 2019; 19: 393-401. https://doi.org/10.1097/ACI.0000000000000539 PMid:31058676
13. Jendoubi F, Gaudenzio N, Gallini A, et al. Omalizumab in the treatment of adult patients with mastocytosis: a systematic review. Clin Exp Allergy 2020; 50: 654-661. https://doi.org/10.1111/cea.13592 PMid:32107810
14. Rossini M, Zanotti R, Orsolini G, et al. Prevalence, pathogenesis, and treatment options for mastocytosis-related osteoporosis. Osteoporos Int 2016; 27: 2411-2421. https://doi.org/10.1007/s00198-016-3539-1 PMid:26892042
15. Rossini M, Zanotti R, Viapiana O, et al. Zoledronic acid in osteoporosis secondary to mastocytosis. Am J Med. 2014; 127: 1127.e1-1127.e4. https://doi.org/10.1016/j.amjmed.2014.06.015 PMid:24954632

16. Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 2015;126:1009-1016. https://doi.org/10.1182/blood-2014-12-614743 PMid:26002962
17. Orsolini G, Gavioli I, Tripi G, et al. Denosumab for the treatment of mastocytosis-related osteoporosis: a case series. Calcif Tissue Int 2017; 100: 595-598. https://doi.org/10.1007/s00223-017-0241-z PMid:28229176
18. Lemal R, Fouquet G, Terriou L, et al. Omalizumab therapy form mast cell-mediator symptoms in patients with ISM, CM, MMAS and MCAS. J Allergy Clin Immunol Pract 2019; 7: 2387-2395. https://doi.org/10.1016/j.jaip.2019.03.039 PMid:30954641
19. Broesby-Olsen S, Vestergaard H, Mortz CG, Jensen B, Havelund T, Hermann AP, Siebenhaar F, Møller MB, Kristensen TK, Bindslev-Jensen C; on behalf of Mastocytosis Centre Odense University Hospital (MastOUH). Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. Allergy 2018; 73: 230-238. https://doi.org/10.1111/all.13237 PMid:28662309
20. Fletcher L, Borate U. Novel approaches for systemic mastocytosis. Curr Opin Hematol 2019; 26; 112-18. https://doi.org/10.1097/MOH.0000000000000486 PMid:30694839
21. van Anrooij B, Oude Elberink JNG, Span LFR, et al. Midostaurin in patients with indolent systemic mastocytosis: an open-label phase 2 trial. J Allergy Clin Immunol 2018; 142: 1006-1008. https://doi.org/10.1016/j.jaci.2018.06.003 PMid:29890238
22. Lortholary O, Chandesris MO, Bulai Livideanu C, et al. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomized, placebo-controlled, phase 3 study. Lancet 2017; 389; 612-20. https://doi.org/10.1016/S0140-6736(16)31403-9
23. Bonadonna P, Bonifacio M, Lombardo C, Zanotti R. Hymenoptera allergy and mast cell activation syndromes. Curr Allergy Asthma Rep 2016; 16: 5. https://doi.org/10.1007/s11882-015-0582-5 PMid:26714690
24. Schuler 4th CF, Volertas S, Khokhar D, et al. Prevalence of mastocytosis and hymenoptera venom allergy in the United States. J Allergy Clin Immunol. 2021 Apr 22:S0091-6749(21)00652-7
25. Golden DBK. Insect sting allergy: new guidelines form the European and USA consensus groups: algorithms and recommendations. Curr Opin Allergy Clin Immunol. 2019 Oct;19(5):456-461 https://doi.org/10.1097/ACI.0000000000000570 PMid:31335358
26. González de Olano D, Alvarez-Twose I, Esteban-López MI, et al. Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. J allergy Clin immunol 2008; 121: 519-526. https://doi.org/10.1016/j.jaci.2007.11.010 PMid:18177694
27. Gruzelle V, Ramassamy M, Bulai Livideanu C, Didier A, Mailhol C, Guilleminault L. Safety of ultra-rush protocols for hymenoptera venom immunotherapy in systemic mastocytosis Allergy 2018; 73: 2260-2263. https://doi.org/10.1111/all.13557 PMid:29984458
28. Valent P., Akin C., Sperr W.R., Escribano L., Arock M., Horny H.P., Bennett J.M., Metcalfe D.D. Aggressive systemic mastocytosis and related mast cell disorders: Current treatment options and proposed response criteria. Leuk. Res. 2003;27:635-641. https://doi.org/10.1016/S0145-2126(02)00168-6
29. Valent P., Akin C., Escribano L., Födinger M., Hartmann K., Brockow K., Castells M., Sperr W.R., Kluin-Nelemans H.C., Hamdy N.A., et al. Standards and standardization in mastocytosis: Consensus statements on diagnostics, treatment recommendations and response criteria. Eur. J. Clin. Investig. 2007;37:435-453. https://doi.org/10.1111/j.1365-2362.2007.01807.x PMid:17537151
30. Pardanani A, Tefferi A. A critical reappraisal of treatment response criteria in systemic mastocytosis and a proposal for revisions. Eur. J. Haematol. 2010;84:371-378. https://doi.org/10.1111/j.1600-0609.2010.01407.x PMid:20059531
31. Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013;121(13):2393-2401. https://doi.org/10.1182/blood-2012-09-458521 PMid:23325841 PMCid:PMC3612852
32. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000; 96: 925-32. https://doi.org/10.1182/blood.V96.3.925 PMid:10910906
33. Ma Y, Zeng S, Metcalfe DD, et al. The c-KIT mutation causing human mastocytosis is resistant to STI571 and other KIT kinase inhibitors; kinases with enzymatic site mutations show different inhibitor sensitivity profiles than wild-type kinases and those with regulatory-type mutations. Blood 2002; 99: 1741-44. https://doi.org/10.1182/blood.V99.5.1741 PMid:11861291
34. Pardanani A, Elliott M, Li CY, Baxter EJ, Cross NCP, Tefferi A. Imatinib for systemic mast-cell disease. Lancet 2003;362(9383):535-6 Lancet 2003 https://doi.org/10.1016/S0140-6736(03)14115-3
35. Droogendijk HJ, Kluin-Nelemans HJ, van Doormaal JJ, Oranje AP, van de Loosdrecht AA, van Daele PL. et al. Imatinib mesylate in the treatment of systemic mastocytosis: a phase II trial. Cancer. 2006 Jul 15;107(2):345-51 https://doi.org/10.1002/cncr.21996 PMid:16779792
36. Vega-Ruiz A et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. Leuk Res 2009;33(11):1481-4 https://doi.org/10.1016/j.leukres.2008.12.020 PMid:19193436 PMCid:PMC4184059
37. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol 2009;84(12):790-4. https://doi.org/10.1002/ajh.21561 PMid:19890907
38. Alvarez-Twose I, Matito A, Morgado JM, et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget 2016;8(40):68950-68963 https://doi.org/10.18632/oncotarget.10711 PMid:28978170 PMCid:PMC5620310
39. Kluin-Nelemans HC, Jansen JH, Breukelman H, Wolthers BG, Kluin PM, Kroon HM, Willemze R. Response to interferon alfa-2b in a patient with systemic mastocytosis. N Engl J Med 1992;326(9):619-23. https://doi.org/10.1056/NEJM199202273260907 PMid:1370856
40. Worobec AS, Kirshenbaum AS, Schwartz LB, Metcalfe DD. Treatment of three patients with systemic mastocytosis with interferon alpha-2b. Leuk Lymphoma 1996;22(5-6):501-8. https://doi.org/10.3109/10428199609054789 PMid:8882964
41. Butterfield JH. Response of severe systemic mastocytosis to interferon alpha. Br J Dermatol 1998;138(3):489-9 https://doi.org/10.1046/j.1365-2133.1998.02131.x PMid:9580806
42. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. Br J Haematol. 2002 Dec;119(4):1090-7 https://doi.org/10.1046/j.1365-2141.2002.03944.x PMid:12472593
43. Hauswirth AW, Simonitsch-Klupp I, Uffmann M, Koller E, Sperr WR, Lechner K, Valent P. Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. Leuk Res. 2004; 28:249-257 https://doi.org/10.1016/S0145-2126(03)00259-5
44. Carrera CJ, Terai C, Lotz M, Curd JG, Piro LD, Beutler E, Carson DA. Potent toxicity of 2-chlorodeoxyadenosine toward human monocytes in vitro and in vivo. A novel approach to immunosuppressive therapy. J Clin Invest 1990;86(5):1480-8 https://doi.org/10.1172/JCI114865 PMid:1700795 PMCid:PMC296893
45. Kirshenbaum AS, Goff JP, Semere T, Foster B, Scott LM, Metcalfe DD. Demonstration that human mast cells arise from a progenitor cell

population that is CD34(+), c-kit(+), and expresses aminopeptidase N (CD13). Blood 1999;94(7):2333-42
https://doi.org/10.1182/blood.V94.7.2333.419k30_2333_2342
PMid:10498605
46. Pardanani A, Hoffbrand AV, Butterfield JH, Tefferi A. Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. Leuk Res 2004 ;28(2):127-31.
https://doi.org/10.1016/S0145-2126(03)00185-1
47. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al. Cladribine therapy for systemic mastocytosis. Blood 2003 ;102(13):4270-6
https://doi.org/10.1182/blood-2003-05-1699
PMid:12933573
48. Verstovsek S, Tefferi A, Cortes J, et al. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clin Cancer Res 2008 ;14(12):3906-15
https://doi.org/10.1158/1078-0432.CCR-08-0366
PMid:18559612 PMCid:PMC5018899
49. Hochhaus A, Baccarani M, Giles FJ, et al. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. J Cancer Res Clin Oncol ;141(11):2047-60
https://doi.org/10.1007/s00432-015-1988-0
PMid:26002753 PMCid:PMC4768228
50. 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):2530-41
https://doi.org/10.1056/NEJMoa1513098
PMid:27355533
51. DeAngelo DJ, George TI, Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia 2018;32(2):470-478
https://doi.org/10.1038/leu.2017.234
PMid:28744009
52. Szudy-Szczyrek A, Bachanek-Mitura O, Gromek T, et al. Real-World Efficacy of Midostaurin in Aggressive Systemic Mastocytosis. J Clin Med 2021 ;10(5):1109
https://doi.org/10.3390/jcm10051109
PMid:33799933 PMCid:PMC7961806
53. Borate U, Mehta A, Reddy V, Tsai M, Josephson N, Schnadig I. Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin. Leuk Res. 2016;44:25-31
https://doi.org/10.1016/j.leukres.2016.02.010
PMid:26994848
54. Gotlib J, Baird JH, George TI, et al. A phase 2 study of brentuximab vedotin in patients with CD30-positive advanced systemic mastocytosis. Blood Adv 2019;3(15):2264-2271
https://doi.org/10.1182/bloodadvances.2019000152
PMid:31350306 PMCid:PMC6693006
55. Deininger MW, Gotlib J, Robinson WA, et al. Avapritinib (BLU-285), a selective KIT inhibitor, is associated with high response rate and tolerable safety profile in advanced systemic mastocytosis: results of a phase 1 study [abstract]. HemaSphere. 2018;2(S1). Abstract PF612
56. DeAngelo DJ, Reiter A, Radia D, et al CT023 - PATHFINDER: Interim analysis of avapritinib (ava) in patients (pts) with advanced systemic mastocytosis (AdvSM) Cancer Res 2021 vol 81 is 13
https://doi.org/10.1158/1538-7445.AM2021-CT023
57. Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol. 2014 Oct 10;32(29):3264-74
https://doi.org/10.1200/JCO.2014.55.2018
PMid:25154823 PMCid:PMC4876356
58. Ustun C, Gotlib J, Popat U, et al. Consensus Opinion on Allogeneic Hematopoietic Cell Transplantation in Advanced Systemic Mastocytosis. Biol Blood Marrow Transplant. 2016 Aug;22(8):1348-1356
https://doi.org/10.1016/j.bbmt.2016.04.018
PMid:27131865
59. Sperr WR, Drach J, Hauswirth AW, et al: Myelomastocytic leukemia: Evidence for the origin of mast cells from the leukemic clone and eradication by allogeneic stem cell transplantation. Clin Cancer Res 2005 11:6787-6792
https://doi.org/10.1158/1078-0432.CCR-05-1064
PMid:16203765
60. Rønnov-Jessen D, Løvgreen Nielsen P, Horn T: Persistence of systemic mastocytosis after allogeneic bone marrow transplantation in spite of complete remission of the associated myelodysplastic syndrome. Bone Marrow Transplant 1991 8:413-415
61. Spyridonidis A, Thomas AK, Bertz H, et al: Evidence for a graft-versus-mast-cell effect after allogeneic bone marrow transplantation. Bone Marrow Transplant 2004 34:515-519.
https://doi.org/10.1038/sj.bmt.1704627
PMid:15273711
62. Gromke T, Elmaagacli AH, Ditschkowski M, et al: Delayed graft-versus-mast-cell effect on systemic mastocytosis with associated clonal haematological nonmast cell lineage disease after allogeneic transplantation. Bone Marrow Transplant 2013 48:732-733
https://doi.org/10.1038/bmt.2012.198
PMid:23085825
63. Nakamura R, Chakrabarti S, Akin C, et al. A pilot study of nonmyeloablative allogeneic hematopoietic stem cell transplant for advanced systemic mastocytosis. Bone Marrow Transplant 2006 37:353-358
https://doi.org/10.1038/sj.bmt.1705245
PMid:16400343