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REVIEW ARTICLE

Catching the clinical and biological diversity for an appropriate therapeutic approach in systemic mastocytosis

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Abstract

Systemic mastocytosis (SM) is a rare disease calling for integrated approaches involving onco-hematologic competences for appropriate clinical management and treatment. The wide variability of manifestations and disease course claims for an accurate risk stratification, currently relying on the appraisal of the benefit/risk ratio of treatment modalities within indolent and advanced variants according to WHO classification. More objective parameters are progressively incorporated and integrated into comprehensive models, on which to support the adoption of therapeutic strategies, since the mere clinical distinction between mediator-related signs/symptoms and "true" organ damage can sometimes be complicated. The development of novel targeted drugs is progressively extending the therapeutic alternatives available, which ranges from conventional agents such as interferon and cladribine, to the more modern approach based on *KIT* inhibition. Ultimately, the choice of the most appropriate therapy should be rationalized on the basis of the clinical picture and molecular data. The focus of the present review is on the areas still open in the current evaluation of SM patients, particularly when considering the need of a treatment.

Keywords Systemic mastocytosis · Prognostic score · Treatment · *KIT* inhibitors

Introduction

The term systemic mastocytosis (SM) denotes a heterogeneous group of disorders featured by abnormal expansion and accumulation of mast cells in several organs. SM is a rare disease that requires integrated approaches involving onco-hematologic expertise for appropriate clinical management and treatment. The wide variability of clinical manifestations and disease course demands for appropriate risk stratification, incorporating objective parameters such as comprehensive molecular profiles. The development of novel targeted drugs is extending progressively the range of available therapeutic alternatives.

The diagnostics of SM relies on the documentation of clonal mast cells through different methodologies, including morphology, histopathology, flow cytometry, molecular genetics, and tryptase assay. Data from diagnostic workout are integrated according to World Health Organization (WHO) [1], as summarized in Table 1. Recent advancements, especially in molecular techniques, have enhanced the diagnostic capability of SM and patients are generally diagnosed and managed earlier compared to one decade ago. That is likely contributing to change our knowledge of the disease rapidly.

General considerations about clinical management

The present review focuses on the still open areas in the current assessment of SM patients, particularly when considering the need of a treatment.

The current paradigm envisions a conservative approach for indolent forms, where life expectancy is not impaired significantly, while cytoreductive treatment is indicated for advanced variants, where the need to control manifestations of myeloproliferation and prevent damage to target organs overtakes the potential side effects of therapies (Fig. 1). Although the clinical manifestations of advanced SM often mandate early initiation of treatment, in other cases the distinction between mediator-related signs/symptoms and "true" organ damage can be complicated. As such, the apparently straightforward

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Table 1 Diagnostic criteria for systemic mastocytosis according to 2016 WHO classification

Major criterion
Multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs
Minor criteria
In biopsy section of BM or other extracutaneous organs, > 25% of mast cells in infiltrates are spindle-shaped or have atypical morphology or, of all mast cells in BM aspirate smears, > 25% are immature or atypical
Detection of an activating point mutation at codon 816 of KIT in BM, blood, or another extracutaneous organ
Mast cells in BM, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers
Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)
Diagnosis of systemic mastocytosis can be made when the major criterion and one minor criterion, or at least three minor criteria, are present

WHO, World Health Organization

dichotomy between indolent and advanced variants has to confront with some challenging subsets often encountered in clinical practice (Fig. 1). In this context, the risk is on one side to overtreat with cytoreductive drugs, on the other to overlook subtle disease-related issues that might deserve a timely therapeutic intervention to avoid further damage. Several biomarkers, including clinical, hematologic, and molecular variables, have been explored, with the aim to provide robust support to clinical management. The inclusion of biological parameters into prognostic models follows this direction. Currently, main therapeutic decisions still rely on the clinical appraisal of the benefit/risk ratio of treatment modalities within indolent and advanced variants according to WHO Classification, with all related limitations to be discussed below.

Prognostic stratification

WHO classification

The combination of mast cell burden and clinical assessment at diagnosis provides the framework for the definition of clinical variants according to 2016 WHO classification [1], as depicted in Fig. 2.

Five prognostically relevant categories are defined: indolent (ISM), smoldering (SSM), SM with an associated hematological neoplasm (SM-AHN), aggressive (ASM), and mast cell leukemia (MCL). Isolated bone marrow mastocytosis (BMM) is considered a provisional sub-entity of typical ISM. ASM, SM-AHN, and MCL are generally grouped as "advanced" SM in order to emphasize their unfavorable prognosis.

The definition of WHO subsets is based on the presence or absence of some findings: "C"-findings relate to mast cell infiltration and organ damage; "B"-findings expresses high mast cell burden without functional consequences.

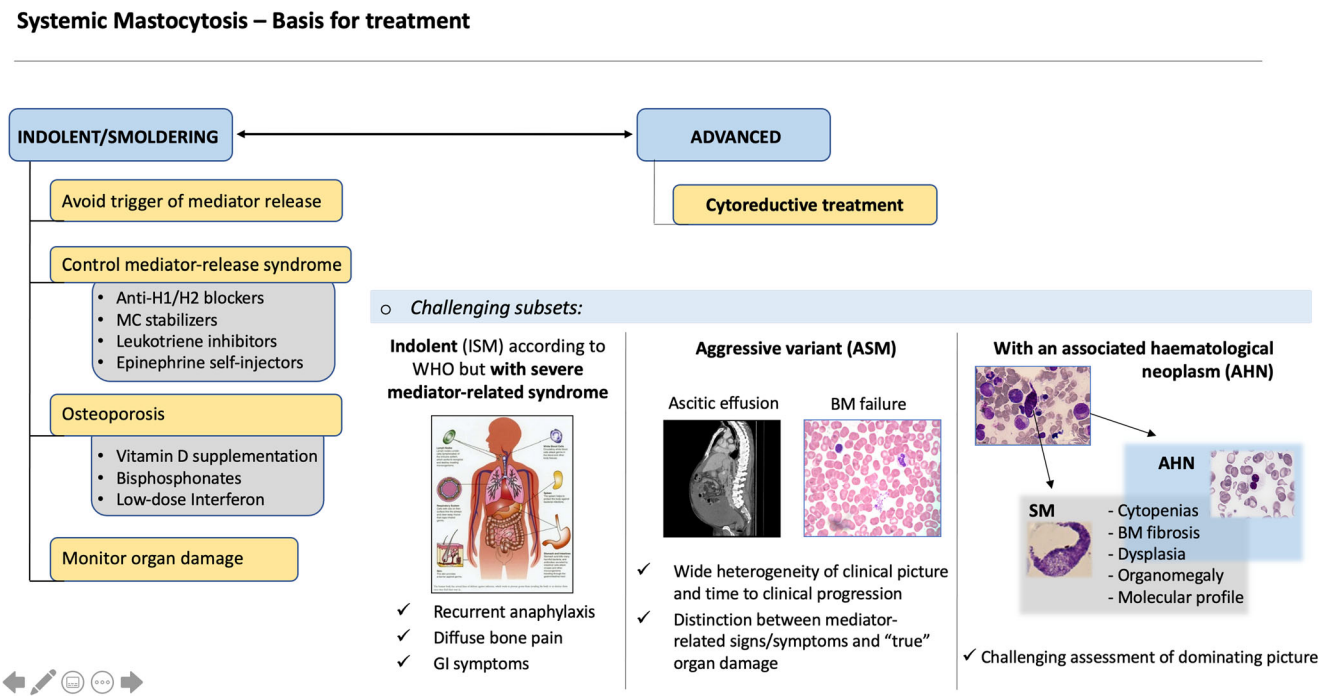

Fig. 1 The basis for treatment of systemic mastocytosis is the distinction between indolent/smoldering from advanced variants according to WHO classification. In routine practice, the clinician often deals with some challenging subsets, where the choice of the most appropriate therapeutic modality should be evaluated carefully in individual cases

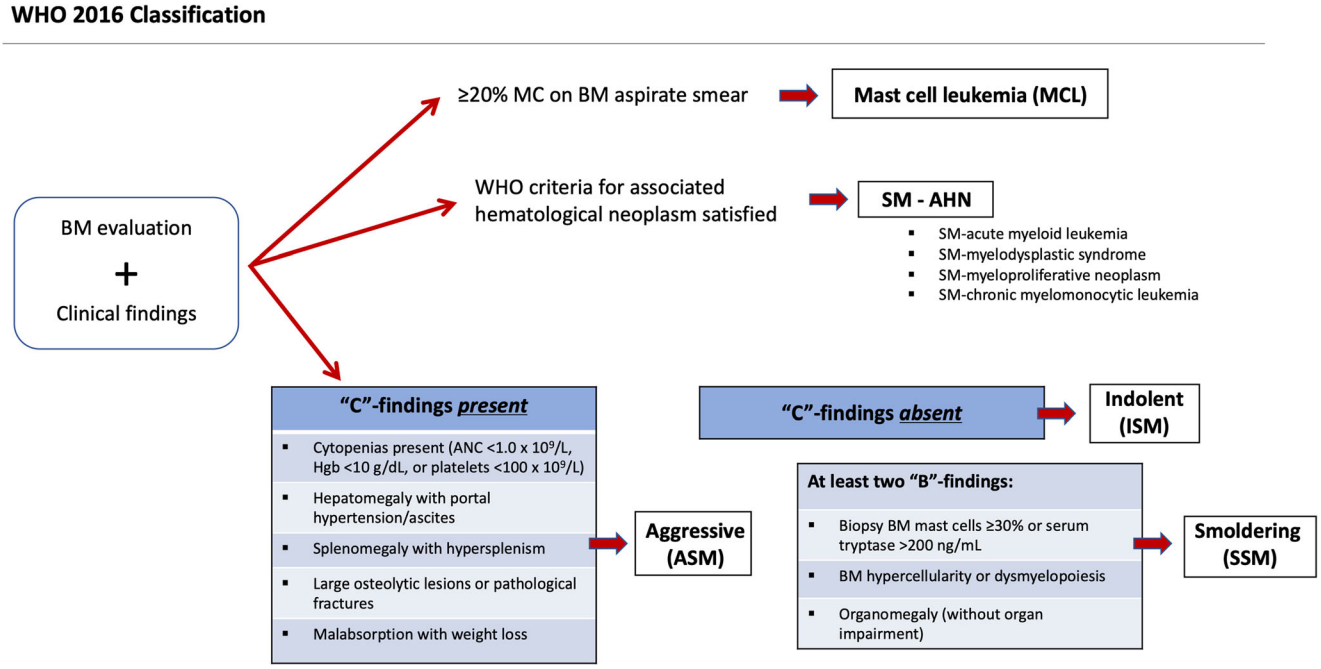

Fig. 2 The integration of data from diagnostic workout and clinical assessment allows the definition of clinical variants according to WHO classification

Although prognostically meaningful [2–4], WHO classification is limited by some relevant flaws. In clinical practice, the distinction between some categories is not always clear-cut and the appraisal of some key parameters may be affected by variable interpretation. Furthermore, all C-findings lead to the definition of ASM subset, but they are clearly featured by wide variability in terms of clinical impact. As an example, the clinical impairment caused by liver involvement and portal hypertension can be much more burdensome than a moderate, stable over-time cytopenia. Often it is not just the organ damage per se, rather it is the time of progression of that impairment (Fig. 1).

The actual prognostic relevance of SSM is debated [5]. In a large retrospective study by European Competence Network on Mastocytosis (ECNM), survival estimates of SSM patients were similar to those of ISM ones [6]. The apparent prognostic weight of disease burden might depend more on age than the specific biological distinction [7].

Another major concern deals with SM-AHN. In this clinical context, SM often accounts for a high-risk, multi-mutated myeloid neoplasm with dismal outcome. However, SM can also accompany relatively indolent disease (such as essential thrombocythemia) and the SM-AHN incidence is likely underestimated, especially when mast cells burden is low. As such, the enrichment in unfavorable cases likely affects the published survival analyses. Despite WHO allocates this category to "advanced" group, in individual cases the SM component should be stratified by B/C-findings in order to estimate its actual clinical impact, even if it can be challenging due to the overlapping with the concomitant AHN (Fig. 1). From a therapeutic standpoint, *KIT* inhibition approach in this setting may lead to different patterns of response depending on the extent of disease addiction to *KIT*. The latter may be potentially estimated by *KIT* allele burden, even if there is no established standard yet [8, 9].

Biomarkers

Several biological parameters have been proposed and tested in SM aiming to an improvement of WHO-based risk stratification.

Multilineage involvement

KIT D816V mutation drives the development of the disease but it is not necessarily restricted to mast cells: Spanish Network on Mastocytosis (REMA) demonstrated the multilineage involvement of the mutation in virtually all patients with ASM and in a proportion of about 20% of ISM cases. Multilineage involvement in ISM was an independent predictor for progression to advanced variants [10]. The assessment of *KIT* mutant in peripheral blood may represent a valid surrogate for multilineage involvement, easing the availability of this important prognostic information [11].

KIT allele burden

The *KIT* D816V expressed allele burden (EAB) strongly correlates with disease features, WHO subtype (indolent vs advanced) and survival [12]. Beyond its association with prognosis, EAB has demonstrated to be a useful tool for the prediction of sustained response in the context of cytoreductive

treatment: the probability of late responses in patients not experiencing at least 25% reduction of EAB at 6 months was very low [8]. This parameter could thus support switching to alternative therapeutic modalities in poor responders, allowing to save time and costs. From a clinical standpoint, a discrepancy between symptom response and disease burden can sometimes be observed, likely because of functional abnormalities of mast cells beyond their mere increased amount. As such, pure quantitative assays may fail to catch all patterns of response to therapy.

Furthermore, mast cells are often underrepresented in bone marrow samples, due to dilution by peripheral blood at aspiration, with consequent underestimation of the disease burden. On this view, Greiner et al recently proposed the measurement of EAB in formalin-fixed, paraffin-embedded bone marrow tissue sections in order to overcome this problem [9].

Molecular genetics

Mutations of genes usually associated with "high-risk" features in myeloid neoplasms [13, 14] are harbored also by a proportion of SM patients and provide clinically relevant information about disease course. In particular, mutations in *SRSF2*, *ASXL1*, *RUNX1* (gathered by the S/A/R acronym), *EZH2* and *CBL* were shown to be prognostically meaningful [7, 15–18]. Of note, these mutations display a markedly different pattern of occurrence across WHO variants: in ISM/SSM, relatively few patients bear additional mutations (around 15%), usually involving *TET2* and *DNMT3A*, commonly found also in clonal hemopoiesis of indeterminate potential (CHIP) [7]. At the opposite, the majority of patients with advanced SM harbor at least 1 "high-risk" mutation (HRM), contributing to further stratify prognostic categories of patients [19].

Of interest, S/A/R profile has been shown to predict poor response to the *KIT* inhibitor midostaurin [8]. These findings open an important question about the role of *KIT* inhibition especially in multi-mutated, myeloid neoplasms, where the efficacy of the approach may be expected to act on the SM component more than on the AHN. The selective pressure exerted by *KIT*-targeted drugs could remodel the clonal architecture of advanced variants, especially of SM-AHN. That clearly supports the concept of treatment combinations (i.e., *KIT* inhibitors plus conventional chemotherapy) to be assessed within clinical trials, wherever a complex molecular background would determine scarce response to targeted agents alone.

Myeloid dysplasia

The presence of hypercellularity or dismyelopoiesis on morphologic assessment of bone marrow is one of the findings used to define the SSM variant [1, 5, 20, 21]. The assessment of these features through morphology can be prone to an operator-dependent variability in interpretation of dysplastic cell features. Multi-parameter flow cytometry (MFC) has been proposed in SM as an effective tool for characterizing abnormalities of antigen expression either on mast cells [22] or residual hematopoiesis [23], providing the opportunity for a more objective appraisal of dysplastic traits.

On that view, MFC abnormalities might also contribute to refine SSM definition, specifically when relying on morphologic dysplasia to meet B-findings.

Integrated prognostic scores

As anticipated, SM is featured by a wide heterogeneity of clinical manifestations and also by plurality of prognostically meaningful parameters, which range from easily attainable assays (hemochrome, alkaline phosphatase, tryptase) to much more complex data (multilineage involvement, high-risk genotype). In recent years, many efforts have been pursued to regulate such a large amount of information, basically in order to provide useful tools for supporting clinical decisions.

To this end, several models incorporating clinical and molecular variables have been devised: the Mayo alliance prognostic system (MAPS) [24], the International prognostic scoring system (IPSM) [4], the Mutation-Adjusted Risk Score (MARS) [25] among the most relevant ones. Some models include clinical information only and are particularly useful in routine practice [4, 24]. Other scores are hybrid, in that add biological, mutational data to clinical ones [24, 25].

The validity of these scores is generally demonstrated on large patient cohorts and also confirmed in external series [4, 26], and they have the undeniable merit to provide a reference framework for SM patient management. However, some limitations have to be acknowledged: data are obtained by retrospective studies, and wide recruitment periods are needed to collect sufficient patients, with all consequent variabilities in terms of diagnostic methods, treatment opportunities, and geographical-related differences in approaches.

Principles of treatment

Indolent/smoldering variants

The general indication for ISM/SSM management envisions a conservative approach, thus not including cytoreductive treatment.

The clinical burden related to mediator release syndrome comprises the whole spectrum from absolute absence of symptoms, to chronic disturbances with a variable impairment of quality of life (fatigue, cutaneous, and gastrointestinal manifestations) up to severe, potentially life-threatening allergic reactions. The use of anti-mediators is generally

recommended for mildly symptomatic patients and the standard therapy consists of histamine receptor blockers (anti-H1 and H2 antagonists) and mast cell stabilizers (sodium cromoglycate, ketotifen), the latter ones especially used in patients suffering from gastrointestinal symptoms. Because of the risk of anaphylaxis, sometimes without an identifiable trigger, SM patients are prescribed to carry epinephrine pen self-injectors and to use the device after an appropriate training in a specialized center. When allergic reactions are due to hymenoptera stings, representing the trigger in up to 50–60% of cases, patients must undergo life-long immunotherapy. If this does not work properly at controlling severe reactions, additional experimental drug therapies such as IgE-depletion (i.e., with omalizumab) must be considered [27].

Some patients experience severe mediators-related symptoms, which are refractory to standard agents: the estimation of the benefit/risk ratio for cytoreduction is particularly challenging in this clinical subset. Few recent studies have explored the use of KIT inhibitors masitinib (randomized, placebo-controlled trial) [28], midostaurin[29], and avapritinib[30] (randomized, placebo-controlled trial) demonstrating an improvement of symptoms with a relatively safe profile. Although reasonable, the feasibility of cytoreductive treatment in this context has not been formally ascertained yet, especially in terms of long-term safety.

A clinically devious manifestation of mediator release is osteopathy, that should be searched for at diagnosis by DEXA-scan. Osteoporosis has not to be interpreted as a sign of disease aggressiveness, but must be promptly identified and managed in order to reduce the risk of bone fractures. When osteoporosis is refractory to conventional agents (vitamin D supplement, bisphosphonates), anti-RANK-ligand antibodies [31] and/or low-dose interferon-alfa can be considered, also due to capability of the latter one to ameliorate the bone density [32, 33].

Advanced variants

As anticipated, the definition of advanced variants gathers different SM forms with highly variable clinical pictures and therapeutic needs. The general statement can only be toward an individualization of treatment, even more important in view of the rapid changes in the therapeutic scenario. Tyrosine kinase inhibitors, progressively more potent and selective, now flank conventional cytoreductive drugs (cladribine, interferon-alfa). The availability of controlled trials comparing such treatment modalities is not expected due to the rarity of the disease, even if the harmonization of response criteria by IWG-MRT might aid to generalize some considerations [34]. Ultimately, the choice of the most appropriate therapy should be rationalized on the clinical picture and molecular data (particularly *KIT* mutational status and high-risk additional mutations). The most relevant therapeutic options are summarized below.

Imatinib

Imatinib has been demonstrated ineffective against the common domain mutant (D816V), but able to induce a response with certain trans-membrane (F522) and juxta-membrane (V560) mutations, at doses ranging from 100 to 400 mg. Although difficult to extract from literature, the response rate is about 30% in *KIT* D816V-negative SM [35]. These findings reasonably support a challenge with Imatinib in this subset (usually for at least 1–2 months, if clinically feasible), taking into account the well-known safety profile from other experiences (i.e., chronic myeloid leukemia). The drug is currently approved for the treatment of adult SM patients without *KIT* D816V or with unknown mutational status.

Cladribine

Cladribine (2-chloro-deoxy-adenosine) has been used in both ISM and advanced variants and the available data are derived from retrospective series, the largest ones from Mayo Clinic [36] and French group [37]. It has been delivered both intravenously and subcutaneously at 0.13–0.17 mg/kg per days for a median number of 3 cycles (up to a maximum of 6). The overall response rate was about 40–50% in advanced forms, positioning the drug as a valid therapeutic option, especially when a rapid debulking is needed, or as salvage therapy. Main concerns derive from the known immunosuppressive effect.

Interferon-alfa

As in the field of myeloproliferative neoplasms, interferon-alfa has shown activity in SM across all clinical variants, with improvement in mediators-related syndrome and in some cases reduction in mast cell burden [27, 38, 39]. It is conventionally employed at 1–3 million units subcutaneously 2–3 times per week and potentially dose-escalated depending on response and tolerability. Late responses have been described, and therapy is generally continued as long as a benefit is observed. The major flaws are the high rate of withdrawal because of scarce tolerance, and the shortfall in availability that has been recently experienced widely. The increasing use of the pegylated formulation in the onco-hematological setting might overcome both issues [40, 41].

Midostaurin

Midostaurin is a multi-kinase inhibitor targeting mutant and wild type *KIT* as well as other kinases such as *FLT3*, *PDGFRA*, and *VEGFR*. The results of a phase 2, non-randomized clinical trial on 89 patients led to drug approval

by regulatory agencies in 2017 for the treatment of adult patients with advanced SM [42]. Midostaurin was given at 100 mg twice daily and showed an overall response rate of 60% according to modified Valent and Cheson criteria [43]. Responses were obtained regardless of *KIT* mutational status or the presence of concomitant AHN. Midostaurin ameliorated also symptom burden [44] and was well tolerated: beyond hematological toxicity, expected for the clinical context, nausea and vomiting were the most frequent adverse events. They were generally manageable with prophylactic antiemetics and assumption with food. A recent update of data after a 10-year follow-up was published: median overall survival was 40 months in the whole cohort and 18.5 months in MCL subset [45]. No relevant long-term toxicities were observed. Midostaurin is thus an effective therapy both as first-line approach, as well as salvage treatment after other cytoreductive therapies.

Allogeneic transplant

Data about the results of allogeneic transplant (HSCT) in SM have been published as case reports or retrospective series, the largest of which including 57 patients transplanted in the USA and Europe [46]. As expected, the cases were enriched for SM-AHN subset, that represented the main reason for allocation to allogeneic HSCT. In other advanced variants, the overall outcome was poor and a diagnosis of MCL was the stronger unfavorable factor for survival. Treatment-related mortality mirrored what seen in other hematologic malignancies.

Given the lack of prospective data, current indications derive from consensus opinion [47]. From a clinical standpoint, the allocation to HSCT is easily sustainable in SM-AHN whenever indicated by AHN component, and in MCL. The decision is much more difficult for patients with advanced SM achieving in-depth responses to Midostaurin or another selective *KIT* inhibitor, since no robust data can favor TKI continuation versus switch to HSCT [48]. No prospective data are available to guide the optimal cytoreductive approach or timing of HSCT. Future guidelines incorporating more accurate risk stratification upon molecular genetics might help clinicians to rationalize this crucial clinical decision.

Investigational agents

Avapritinib/BLU-285

The drug is a kinase inhibitor featured by high selectivity for *KIT* mutant and limited off-target activity. The interim analysis from phase 1 study (Explorer trial; NCT02561988) showed a promising overall response rate of 83%, observed across all SM subtypes, with relatively good tolerability and short time to evidence of a clinical response. A phase 2 study (NCT03580655) is currently enrolling advanced SM cases [48]. Of interest, almost 90% of patients achieved a reduction of at least 50% in *KIT* D816V allele burden, and up to one-third of patients exhibited a complete molecular remission using digital droplet PCR, indicating a great potency against *KIT* molecular target (estimated in vitro to be as 10-fold greater than Midostaurin) [48].

Ripretinib/DCC-2618

It is a potent inhibitor of *KIT* exon 17 mutants that is currently investigated within a phase 1, open-label trial (NCT02571036).

Considerations about SARS-CoV-2 pandemic

Several concerns have been raised in the clinical management of SM patients due to the pandemic by SARS-CoV-2 infection. Some points have been set by a group of international experts in order to provide a reference for clinicians that are daily involved with patients [49]. At the time of writing, there is no reason to conclude that SM patients have a higher risk to acquire a SARS-CoV-2 infection.

The risk of progression of COVID-19 to severe pneumonia, with acute respiratory distress syndrome (ARDS), remains unknown in patients with SM. However, in advanced SM this risk may be increased for several reasons. There is no definitive evidence so far to suggest SM patients to be at higher risk for developing severe COVID-19 disease because of treatment. Whenever possible, glucocorticoids and cytoreductive drugs should be dose-reduced or postponed. However, there are no published data about the impact of such treatment during an active COVID-19 infection [49].

Conclusions

SM gathers a group of rare disorders affecting several organs with different mechanisms, either mediators-related or depending on direct infiltration by neoplastic mast cells. The extreme heterogeneity of clinical manifestations makes particularly uncomfortable the role of the clinician hematologist, often suspended between the risk of overlooking and overtreating. A multiplicity of parameters, clinical and biological, have demonstrated to influence the risk of progression and overall outcome: the most objective among them (molecular genetics *in primis*) are progressively providing a guide for the selection of the appropriate therapeutic modalities. *KIT* inhibition currently represents the emerging approach, but also its use needs to be adapted upon the clinical/biological context. Severe mast cell activation syndrome and advanced, multi-mutated SM variants still present many unresolved

issues to be tackled in the next future, ideally within prospective clinical trials.

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Compliance with ethical standards

Conflict of interest FM received honoraria for participation to advisory board and speaker bureau from Novartis Pharmaceuticals.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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