Systemic mastocytosis is a heterogeneous disease characterized by the accumulation of neoplastic mast cells in the bone marrow and other organ organs/tissues. Mutations in KIT, most frequently KIT D816V, are detected in over 80% of all systemic mastocytosis patients. While most systemic mastocytosis patients suffer from an indolent disease variant, some present with more aggressive variants, collectively called “advanced systemic mastocytosis”, which include aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic, clonal non mast cell-lineage disease, and mast cell leukemia. Whereas patients with indolent systemic mastocytosis have a near normal life expectancy, patients with advanced systemic mastocytosis have a reduced life expectancy. Although cladribine and interferon-alpha are of benefit in a group of patients with advanced systemic mastocytosis, no curative therapy is available for these patients except possible allogeneic hematopoietic stem cell transplantation. Recent studies have also revealed additional somatic defects (apart from mutations in KIT) in a majority of patients with advanced systemic mastocytosis. These include TET2, SRSF2, ASXL1, RUNX1, JAK2, and/or RAS mutations, which may adversely impact prognosis and survival in particular systemic mastocytosis with an associated hematological neoplasm. In addition, several additional signaling molecules involved in the abnormal proliferation of mast cells in systemic mastocytosis have been identified. These advances have led to a better understanding of the biology of advanced systemic mastocytosis and to the development of new targeted treatment concepts. Herein, we review the biology and pathogenesis of advanced systemic mastocytosis, with a special focus on novel molecular findings as well as current and evolving therapeutic options.
Introduction

Mastocytosis comprises a pathomorphologically and clinically heterogeneous spectrum of localized or systemic disorders characterized by an abnormal accumulation of mast cells (MCs) in one or more organs. In children, the disease is mostly restricted to the skin (cutaneous mastocytosis: CM). By contrast, adult patients usually present with systemic mastocytosis (SM). In patients with SM, neoplastic MCs are almost always detectable in the bone marrow (BM), and usually also in other internal organs. The exact incidence of SM remains uncertain, but a prevalence of mastocytosis including all the subtypes is estimated to be approximately 1 in 10,000 people. A recent study from Denmark showed the incidence rate for all SM, including CM, was 0.89 per 100,000/year.

The World Health Organization (WHO) classification has defined major categories and variants of SM (Online Supplementary Table S1). Most adult patients present with indolent SM (ISM), which is mainly characterized by mediator-related symptoms, frequent skin involvement, no organ dysfunction and a nearly normal life expectancy. By contrast, in advanced variants of the disease (AdvSM), including SM with an associated clonal hematologic non-MC lineage disease (SM-AHNMD; recently updated to systemic mastocytosis with an associated hematological neoplasm (SM-AHN) by WHO), aggressive SM (ASM), and mast cell leukemia (MCL), the malignant expansion and accumulation of neoplastic MCs can lead to organ damage (“C-findings”, Online Supplementary Table S2). No skin lesions are found in some patients. Depending on the subtype, the survival of patients with AdvSM ranges from a few months to several years, therefore cytoreductive therapy is indicated in most of these patients.

Response criteria were developed (Online Supplementary Table S3), and updated and detailed for clinical trials by a consensus group.

Molecular defects found in advanced systemic mastocytosis KIT mutations and their sensitivity to tyrosine kinase inhibitors

KIT is a type III tyrosine kinase (TK) transmembrane receptor for stem cell factor (SCF), which is the major growth factor of MCs in humans (Figure 1). Interestingly, in most cases of SM (overall >80%, in typical ISM >90%, and in AdvSM >70%), an acquired point mutation in the gene coding for KIT (CD117) is found. Although KIT D816V, an activation loop mutation, is the most common mutation found, more than 20 other mutations in KIT have been described in SM. The exact percentages vary, depending on disease subtypes (e.g. ISM vs. ASM) and cell source [e.g. BM vs. peripheral blood (PB)]. The KIT D816V mutation is detected in AHN cells in the majority of cases, which reflects multilineage involvement. There are, however, cases in which two independent subclones exist and this might depend on the type of AHN. KIT mutations often cause ligand-independent constitutive phosphorylation and activation of KIT, which transforms cell lines from factor-dependent growth to factor independence and tumorigenicity. Longley et al. proposed to divide activating mutations of KIT into two types: “regulatory type” mutations affecting regulation of the kinase molecule, and “enzymatic pocket type” mutations, which change the amino acid sequence of the enzymatic site. These latter mutations induce stabilization of the activation loop in an active conformation and/or structural alteration at the ATP-binding site of KIT, resulting in a decreased affinity for type I TK inhibitors (TKI), such as imatinib, that recognize the active conformation of a kinase. The MCL-like cell line HMC-1 has developed two sub-clones: HMC-1.1 which harbors a juxtamembrane domain (JMD) regulatory type mutation, KITV560G, and HMC-1.2 expressing both KIT D816V and KITV560G. Imatinib inhibits only the regulatory type mutant affecting the juxtamembrane inhibitory helix, but does not significantly inhibit KIT D816V. However, even some JMD-type KIT mutations (e.g. KITV559I) can cause imatinib resistance by leading to structural changes of the JMD of KIT, which affects the structure of the kinase domain. Other TKIs, such as PKC412 (midostaurin) effectively suppress the activity of imatinib-resistant KIT mutants.
note, the allele burden of the KIT mutant, determined by highly sensitive techniques, such as allele specific quantitative PCR (ASO-qPCR), correlates with the burden of neoplastic MCs, and with survival and prognosis.\textsuperscript{15,36,37} Finally, although the KIT D816V mutant is recurrently found in SM patients, a recent report has pointed to the possibility that such patients may present with concurrent mutations in other codons of the KIT gene.\textsuperscript{38} Indeed, out of 21 patients analyzed, the authors found 3 (15\%) patients with KIT D816V and a concurrent mutation.\textsuperscript{38} Overall, these data suggest an advantage for double mutations that might contribute to the aggressiveness of SM.

**Tyrosine kinase inhibitors (TKI)**

*Midostaurin (PKC412):* Midostaurin (PKC412) is an oral multi-kinase inhibitor with activity against protein kinase C (PKC), FMS-related tyrosine kinase 3 (FLT3), PDGFRa/B, vascular endothelial growth factor receptor 2 (VEGFR-2), and KIT. Midostaurin was evaluated in a centrally adjudicated, phase II multi-center international study in 116 patients with ASM, of which 89 were evaluable for efficacy.\textsuperscript{39} Overall, 73 patients (82\%) had ASM, 16 (18\%) had MCL, and 63/89 patients (71\%) had an AHN. Seventy-seven patients (87\%) were positive for a codon 816 KIT mutation. After a median follow-up of 26 months (range 12-54 months), the overall response rate (ORR) was 60\%. Most responses were major (75\%), including decreases of >50\% in serum tryptase and BM mast cell levels. These responses were durable: the median duration of response and median OS were 24.1 and 28.7 months, respectively. Median OS was 9.4 months in patients with MCL; however, responders in the MCL group did not reach a median OS. Midostaurin was tolerated fairly well with grade 1-2 gastrointestinal side effects being the most common adverse events (Table 1). Patient-reported outcomes, including symptoms and quality of life, measured by the Memorial Symptom Assessment Scale and the Short Form-12 Health Survey, respectively, significantly improved with midostaurin therapy. These results indicate that the drug has a favorable efficacy and safety pro-

### Table 1. Treatment and outcomes in advanced SM

<table>
<thead>
<tr>
<th>Author, (Reference)</th>
<th>Therapy</th>
<th>Patient(^a)</th>
<th>Study Type</th>
<th>Complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vega-Ruiz(40)</td>
<td>Imatinib</td>
<td>20 with ISM or AdvSM (n=9)</td>
<td>Prospective, Phase II</td>
<td>Grade IV: Thrombocytopenia 5% Neutropenia 5% Symptomatic improvement, 30% Median OS was NR</td>
<td>CR, 5%</td>
</tr>
<tr>
<td>Verstovsek(50)</td>
<td>Dasatinib</td>
<td>33 with ISM or AdvSM (n=15)</td>
<td>Prospective, Phase II</td>
<td>Grade III/IV: Neutropenia 5% Leukopenia 4% Anemia 3% Febrile neutropenia 3% Thrombocytopenia 3%</td>
<td>ORR, 33% CR, 6.6% Median OS was NR</td>
</tr>
<tr>
<td>Gotlib(39)</td>
<td>Midostaurin</td>
<td>116 with AdvSM</td>
<td>Prospective, Phase II</td>
<td>Grade IV/IV: Neutropenia 5% Leukopenia 4% Anemia 3% Febrile neutropenia 3% Thrombocytopenia 3%</td>
<td>ORR, 60% MR, 75% IR, 36% PCR, 28% Unspecified, 11% Good PR, 21% Minor PR, 4%</td>
</tr>
<tr>
<td>Kluin-Nelemans(119)</td>
<td>Cladribine</td>
<td>10 with ISM and AdvM (n=6)</td>
<td>Prospective</td>
<td>Cytopenia All patients responded, no CR</td>
<td>Median OS was NR</td>
</tr>
<tr>
<td>Barete(123)</td>
<td>Cladribine</td>
<td>68 with ISM and AdvSM (n=32)</td>
<td>Retrospective, registry study with a long follow-up (&gt;10 years)</td>
<td>Grade III/IV: Lymphopenia 82% Neutropenia 47% Infections 13%</td>
<td>ORR, 72%, No CR ORR in AdvSM 50%</td>
</tr>
<tr>
<td>Ustun(125)</td>
<td>Allo-HCT</td>
<td>57 with Adv SM</td>
<td>Retrospective</td>
<td>TRM at 6 months: 11%</td>
<td>OS at 3 years: 57% SM-AHN: 74% ASM: 43% MCL: 17% DFS at 3 years: 51% SM-AHN: 63% ASM: 43% MCL: 17%</td>
</tr>
</tbody>
</table>

\(\text{AHN: associated hematological neoplasm; Adv-SM: advanced systemic mastocytosis; AE: adverse event; Allo-HCT: allogeneic hematopoietic cell transplantation; CR: complete remission; DFS: disease-free survival; IR: incomplete remission; ISM: indolent systemic mastocytosis; MCL: mast cell leukemia; Mos, months; MR: major response; NR: not reported; ORR: overall response rate; OS: overall survival; PCR, pure clinical response; PR: partial response; SM: systemic mastocytosis; TRM: transplant-related mortality.}\)
file with activity in AdvSM regardless of KIT mutation status. Although midostaurin has not been approved by major drug authorities in either Europe or the USA, it is available for patients with AdvSM within a compassionate use program sponsored by the drug company.

Imatinib: After the remarkable success of TKIs in chronic myeloid leukemia (CML), significant enthusiasm for TKI in the treatment of SM emerged in the early 2000s. However, imatinib is largely ineffective in patients with KIT D816V SM. On the other hand, some patients with SM may respond very well to imatinib, especially with other KIT mutations such as K509I, F522C or KIT WT. In patients with FIP1L1-PDGFRα-positive myeloid neoplasms with eosinophilia, small doses of imatinib (100 mg/d) will effect durable hematologic and cytogenetic/molecular remission in almost all cases. Although some of these patients may exhibit scattered/interstitial distributions of increased abnormal CD25+ MCs in the BM, these cases are not considered a subtype of SM by the WHO because typical dense infil- trates and quality of life). ORR was 56% by AFIRMM (i.e. disabilities associated with flushes, depression, pruri-
tus against masitinib. In one study, masitinib was adminis-
trated in patients with SM-AHN25,64,65 and preceded KIT D816V in these patients.25 The frequency of
KIT D816V mutations in AdvSM is low, ranging from 0 to 5%. U2AF1 mutations are less frequently reported in SM.

Mutations in TET2, also detected in healthy individu-
als, cause loss of function (i.e. regulating gene expression at the cellular level), and are associated with increased self-renewal capacity of hematopoietic stem cells. Recently, several investigators have identified TET2 mutations scattered across several of its 12 exons in 1 or both TET2 alleles, as an early event during the development of various malignancies. Patients with mutant TET2+ myeloid disorders show a decreased level of 5-hmc with hypomethylation or hypermethylation of DNA. Altogether these data show that TET2 plays a role in various hematologic malignancies. In line with these recently published data, TET2 mutations have been reported in 20-40% of KIT D816V-positive AdvSM patients. The cooperation between KIT D816V and loss of function of TET2 in MC results in transformation to a more aggressive disease phenotype in mice. It has also been suggested that TET2 mutations can occur before KIT D816V in ASM-AHN patients. Thus, the acquisition of KIT D816V might act as a phenotype modifier of ASM in these cases. Patients carrying a combination of TET2 and DNMT3A (a DNA methyltransferase) mutations have a poor prognosis compared to those with wild-type genes. In vitro, a combi-
nation of dasatinib and decitabine (a hypomethylating agent) was more effective at inducing apoptosis and cell death in HMC-1.2 cells harboring a TET2 mutant compared to each compound alone. This combination also had less effect in TET2 wild-type cells due to a lower effi-
cacy of decitabine. The impact of TET2 mutations on overall survival remains uncertain. The spliceosome machinery includes SRSF2, U2AF1, and SF3B1 proteins, and is involved in the removal of introns from a transcribed pre-mRNA. Mutations in the spliceosome machinery have recently been identified using whole exome/genome technologies in MDS and MPN. A mutation in the hotspot region of SRSF2 (codon P95) is found in approximately 1/3 of AdvSM patients but is usually not detectable in patients with ISM or SSM. It is more common in ASM-AHN and precedes KIT D816V in these patients. The frequency of SF3B1 mutations in AdvSM is low, ranging from 0 to 5%. U2AF1 mutations are less frequently reported in SM.

The gene ASXL1 (additional sex combs–like 1) encodes for a protein of the polycomb group and trithorax complex family, which interacts with retinoic acid receptor and may be involved in chromatin remodeling. The presence of ASXL1 mutations has been reported in SM at various frequencies, and alone or with other mutations seems to be a poor prognostic factor for OS in patients. ASXL1 mutations are less frequently reported in SM.

The gene ASXL1 (additional sex combs–like 1) encodes for a protein of the polycomb group and trithorax complex family, which interacts with retinoic acid receptor and may be involved in chromatin remodeling. The presence of ASXL1 mutations has been reported in SM at various frequencies, and alone or with other mutations seems to be a poor prognostic factor for OS in patients.
are found in AdvSM, but not in ISM or SSM. The frequency of RAS mutations (e.g. NRAS, KRAS or HRAS) in SM has been investigated, with KRAS and NRAS mutants being found in AdvSM at a relatively low frequency, and not usually detectable in patients with ISM.

The presence of additional genetic defects in KIT D816V+ AdvSM patients may confer adverse prognosis as compared with patients without such abnormalities. In a recent study, Jawhar et al. have analyzed the impact of several additional defects on 70 multi-mutated KIT D816V+ patients with an AHN. In this study, the most frequently identified mutated genes were TET2 (n=38 of 70 patients), SRSF2 (n=30), ASXL1 (n=20), RUNX1 (n=16) and JAK2 (n=11). In multivariate analysis, SRSF2 and ASXL1 remained the most predictive adverse indicators concerning OS. Furthermore, the authors found that inferior OS and adverse clinical characteristics were significantly influenced by the number of mutated genes in the SRSF2/ASXL1/RUNX1 (S/A/R) panel (P<0.0001).

It appears that, based on these findings, the inclusion of molecular markers should be considered in upcoming prognostic scoring systems for patients with SM. This might be particularly important for patients with SM-AHN given that most of these studies were done in patients with SM-AHN. Although it is arguable that these mutations could be detected due to the copresence of an AHN, there are recent studies in pure SM showing these mutations as well. In addition, it has been described in many previous reports that KIT mutations are not restricted to the mast cell disease components in SM-AHN. Although we are at an early stage in the understanding of the clinical and biological importance of these mutations in SM, most likely these mutations affect hematopoietic stem and progenitor cells, and the rate of multilineage involvement increases with the aggressiveness of SM.

In addition, recent investigations on mutational profiles of colonies grown from granulocyte-macrophage colony-forming progenitor cells (CFU-GM) and microdissected mature cells (tryptase or CD15 positive) revealed that forming progenitor cells (CFU-GM) and microdissected hematopoietic stem and progenitor cells, and the rate of multilineage involvement increases with the aggressiveness of SM.

Critical intracellular pro-oncogenic pathways in neoplastic mast cells as novel potential therapeutic targets

Several studies have reported that the ability of wild-type and oncogenic mutant forms of KIT to induce signal transduction differs not only quantitatively but also qualitatively. These altered pathways, which are presented in Figure 3 together with potential targeted drugs, may have an effect on several properties of neoplastic MCs by reducing apoptosis and/or by inducing alterations in the cell cycle.

MCL-1, a BCL-2 family member with anti-apoptotic properties, is expressed in primary neoplastic MCs in SM as well as in the HMC-1.1 and HMC-1.2 cell lines. The targeting of MCL-1 by antisense oligonucleotides (ASOs) or MCL-1-specific siRNA resulted in reduced survival and increased apoptosis in these cell lines. Moreover, MCL-1 ASOs cooperated with various KIT-targeting TKIs in producing growth inhibition in neoplastic MC lines.

BIM, a pro-apoptotic member of the BCL-2 family, has been identified as a tumor suppressor in neoplastic MCs. BIM is downregulated in neoplastic MCs by SCF as well as by KIT D816V. Midostaurin, bortezomib (a proteasome inhibitor), and obatoclax (a pan-BCL-2 family blocker) reportedly upregulate BIM expression in HMC-1 cells and may thereby promote apoptosis. Obatoclax also increased apoptosis in these cells.

Activated LYN and BTK are expressed in neoplastic MCs in a KIT-independent manner in patients with ASM and MCL, and may thus contribute to malignant transformation. LYN is a member of the SRC family involved in cellular signaling processes regulating growth, differentiation, and apoptosis. Activated LYN regulates BTK function and may influence the process of degranulation and cytokine production in MCs. Dasatinib and bosutinib (SRC inhibitors) disrupt LYN and BTK activation and oncogenic signaling in neoplastic MCs. Bosutinib inhibits the growth of neoplastic MCs in vitro at relatively high concentrations, with no effect on KIT. Bosutinib acts synergistically with midostaurin on HMC-1 cell proliferation. However, bosutinib is unable to induce any response in patients with AdvSM.
Phosphoinositide 3-kinase (PI3-K), a lipid kinase, is important for the function of intracellular signaling molecules, like BTK, AKT and PDK1, by inducing phosphatidylinositol 3,4,5-trisphosphate (PIP3) that provides membrane docking sites for these signaling molecules. In both HMC-1 subclones (HMC-1.1 and HMC-1.2), mutated KIT leads to constitutive activation of PI3-K. Once activated, the PI3-K subsequently activates AKT, a key signaling molecule involved in KIT-dependent differentiation and growth of neoplastic MCs harboring oncogenic KIT mutants. Indeed, AKT was found to be phosphorylated in neoplastic MCs in patients with KIT D816V+ SM and in the HMC-1.2 cell line.

PI3-K and AKT are also important for the regulation of the mammalian target of rapamycin (mTOR), a serine/threonine kinase that interacts with 2 regulatory protein complexes called mTOR complex 1 (mTORC1) and complex 2 (mTORC2). PI3-K regulates the mTORC1 pathway via the activation of AKT which directly activates tuberin, the inhibitor of mTOR activation. Once activated, mTORC1 phosphorylates p70 ribosomal S6 kinase (p70S6K), resulting in increased gene transcription that regulates cell growth, survival, protein synthesis and metabolism. Smrz et al. showed that the expression and activation of mTORC1 and mTORC2 was increased in neoplastic human MC lines and in immature normal MCs, as compared with mature normal MCs. Interestingly, the authors demonstrated that mTORC1 might contribute to MC survival, while mTORC2 might only fulfill critical functions in the context of proliferating (dividing) neoplastic MCs harboring oncogenic KIT mutations. Indeed, AKT was found to be phosphorylated in neoplastic MCs in patients with KIT D816V+ SM and in the HMC-1.2 cell line.

Figure 3. Intracellular pathways involved in the accumulation/proliferation of neoplastic mast cells in SM and agents which could be potentially used to target one or the other of these molecules. That KIT D816V dimerizes spontaneously with itself or with KIT WT, or is capable of transmitting oncogenic signals as a single molecule, remains largely unexplored. However, it has been postulated whether the KIT D816V protein could activate substrates under a monomeric form and could even be located in the cell cytoplasm. The KIT D816V oncogenic mutation alters the substrate specificity of the mutant protein, which shows a substrate specificity resembling that of SRC and ABL TKs. In addition, FES TK is activated by mutant KIT protein and negatively regulates the STAT pathway, although it induced phosphorylation of mTOR. Furthermore, AKT activation has been identified as a key signaling molecule involved in KIT D816V-dependent differentiation and growth of neoplastic MCs. Also, STAT5 is believed to play a pivotal role in the growth of KIT D816V+ neoplastic MCs and is constitutively phosphorylated in such cells, probably because KIT D816V can promote direct STAT5 activation, thus diverting the canonical JAK-STAT pathway. A number of drugs (in red and in italics) can potentially selectively inhibit some of these critical pathways. Red arrows: inhibition; black arrows: induction of survival or functions; green arrows: activation of signaling pathways; dark blue arrow: induction of increased synthesis.
STAT5 an attractive target for therapy in AdvSM. However, until now, most drugs targeting STAT5 exert anti-neoplastic effects only at high, non-pharmacological concentrations in vitro. The inhibition of the JAK-STAT signaling pathway in vitro decreased KIT D816V-mediated cell growth. Ruxolitinib, a JAK1/2 inhibitor, has shown clinical benefit in patients with MPN regardless of JAK2 V617F-mutation. Ruxolitinib decreased spleen size and improved blood counts in a KIT-mutated but not JAK2 V617F-mutated patient with SM-MPN primary myelofibrosis. Therefore, JAK1/2 blockers can be considered in studies of patients with SM-MPN.

NF-κB, a dimeric transcription factor of the REL family, was found to be spontaneously activated in HMC-1 cells. IMD-0354 inhibited translocation of NF-κB to the nucleus, and thus led to decreased cyclin D3 expression and increased cell cycle arrest in HMC-1 cells in vitro. Another transcription factor of the REL family, nuclear factor of activated T cells (NFAT), has also been found constitutively activated in KIT-mutated neoplastic MCs. The combination of a KIT inhibitor and of a calcineurin phosphatase inhibitor (a NFAT regulator) exhibited a synergistic inhibitory effect on cell viability and survival in KIT-mutated MC lines.

One promising class of targets within chromatin regulatory molecules and related antigens are the bromodomain (BRD)-containing proteins. Indeed, inhibition of the epigenetic reader bromodomain-containing protein-4 (BRD4) by exposure to RNA interference or treatment with JQ1, a drug blocking the specific interactions between BRD4 and acetylated histones, resulted in major antileukemic effects in murine and human AML cells. More recently, BRD4 has been identified as a novel drug target in AdvSM. The authors showed that neoplastic MCs expressed substantial amounts of BRD4 in ASM and MCL, as assessed by immunohistochemistry and PCR.
They also reported that the human MCL lines HMC-1 and ROSA also expressed BRD4, and that a BRD4-specific short hairpin RNA or the BRD4-targeting drug JQ1 induced dose-dependent growth inhibition and apoptosis in HMC-1 and ROSA cells, regardless of the presence or absence of the KIT D816V mutant.104 Moreover, the authors demonstrated that JQ1 suppressed the proliferation of primary neoplastic MCs obtained from patients with ASM or MCL. Finally, in drug combination experiments, midostaurin (PKC412) and all-trans retinoic acids were found by the authors to cooperate with JQ1 in producing synergistic effects on survival in HMC-1 and ROSA cells.105 Taken together, these data identified BRD4 as a promising drug target in advanced SM. However, whether JQ1 or other BET bromodomain inhibitors are effective in vivo in patients with AdvSM remains to be elucidated.

Antibody-mediated therapeutic approach to target neoplastic mast cells and stem cells

Based on recent knowledge on the phenotype of malignant MCs and their neoplastic progenitors, a number of cell surface antigens might be aberrantly expressed, including CD13, CD25, CD80, CD83, CD44, CD52, CD87, and CD117, and therefore might be considered also as potential targets of therapy in AdvSM.106,110 For example, neoplastic MCs and their progenitors have been shown to respond in vitro to gemtuzumab ozogamicin (a monoclonal antibody targeting CD33 combined to a cytostatic agent).111 The CD52-targeting antibody alemtuzumab induces cell death in neoplastic MCs in vitro and in mice xenotransplanted with HMC-1 cells.106 CD30 is expressed on the surface of neoplastic MCs in a proportion of patients with AdvSM, but not on normal/reactive MCs, making this antigen an attractive target of specific therapy in these patients.107,112,113 A single-arm, open-label clinical trial applying brentuximab vedotin (SGN-35) to patients with CD30-positive AdvSM (clinicaltrials.gov identifier: N1807598) is ongoing in the US. Neoplastic (leukemic) stem cells (LSCs) have recently been identified in AdvSM. These cells reside within a CD34+ cell fraction and co-express aminopeptidase N (CD13), leukosialin (CD43), Pgp-1 (CD44), the IL-3R α-chain (CD123), AC153 (CD133), CXCR4 (CD184), CD33, CD52 and CD117.114,115 As observed in chronic myeloid leukemia, a part of these LSCs might be non-cycling and therefore probably resistant to treatment with TKIs. Thus, a combination of a TKI that targets KIT on neoplastic MCs and a mAb targeting a surface antigen, such as CD52 for instance, expressed on non-cycling LSCs, may help to achieve a minimal residual disease negative state in AdvSM.

Conventional therapies with anti-neoplastic drugs and allogeneic hematopoietic cell transplantation

Cytarabine, fludarabine, hydroxyurea (a drug of choice in palliative care)105 and interferon-alpha (IFN-α)116-118 have been frequently used for cytoreduction in the treatment of AdvSM. Hydroxyurea is useful to control leukocyte counts in AdvSM, especially in SM-AHN (palliative therapy) and in patients with comorbidity. Cladribine (2-CDA) is the most effective and frequently used drug. Kluin-Nelemans et al., used 2-CDA in 10 patients with SM, most of them suffering from AdvSM (Table 1).119 All patients responded concerning clinical symptoms and MC burden as reflected in declining serum tryptase values and urinary histamine metabolite excretion. Although no patient achieved a complete remission (CR), clinically meaningful and some durable responses were seen, suggesting that 2-CDA may be a potentially effective treatment option for some patients with severe SM.119 These results have been supported by more recent studies.120-123 For instance, in a study on 44 SM patients, the median duration of response was 20 months; however, none of the patients with SM-AHN responded.122 However, 2-CDA usually does not control the disease for prolonged periods of time in rapidly progressing ASM and MCL. For these patients, more intensive therapy, such as AML-like multi-agent chemotherapy, including fludarabine and cytarabine124 should be considered in induction therapy and then for allogeneic hematopoietic cell transplantation (HCT) for consolidation therapy.125-127 Allogeneic HCT remains the only potentially curative treatment option for patients with AdvSM. We have recently reported data on the effect of allo-HCT in patients with AdvSM (Table 1).123 Most patients (the median age was 46) received a graft from HLA-identical siblings (n=34) or unrelated donors (URD) (n=17). Overall survival (OS) and SM progression-free survival (PFS) at 3 years for all patients were 57% and 51%, respectively. They were significantly affected, however, by the type of advanced SM: 74% and 63%, respectively, for SM-AHN; 43% and 43%, respectively, for ASM; and 17% and 17%, respectively, for MCL. Although the data presented are very encouraging, future prospective studies, perhaps per recommended consensus opinion to homogenously collect data,128 are required to confirm the safety129 and efficacy of this treatment approach in AdvSM.

Miscellaneous aspects of management in AdvSM

Patients with SM-AHN should be treated according to generally accepted guidelines: the SM component of the disease is treated as if no AHN was diagnosed, and the AHN component of the disease is treated as if no SM was diagnosed, with the recognition of potential drug interactions107,115 deciding whether the SM or AHN component is primarily contributing to organ damage or other related clinical, labatory concerns. However, admittedly it is often not possible to clearly delineate whether one or the other component is responsible for the clinical issues/organ damage.

As a supportive therapy, H1-receptor antagonists, such as the classical antihistamine hydroxyzine, or non-sedating antihistamines, such as loratadine or fexofenadine, can be administered for the alleviation of symptoms caused by the release of the mediators (e.g. pruritus and flushing).130-132

Conclusion and perspectives

Advanced variants of SM share two major characteristics: i) the prognosis of the disease remains poor, and ii) other than allogeneic HCT no curative therapy is available. Only a few drugs have shown beneficial effects in AdvSM (2-CDA, interferon-alpha, and midostaurin). We propose a treatment algorithm with current therapy options (Figure 4). However, this is a subject to change in the future due to remarkable progress in the biology of AdvSM. Neoplastic cells in SM are usually driven by a canonical KIT-downstream pathway as well as by addi-
tional somatic mutations and KIT-independent pathways and molecules, including TET2, the spliceosome machinery, ASXL1, or RAS. We may better prognosticate AdvSM using these additional genetic defects. The PI3-kinase, AKT, STAT-5, BTK, FES, mTORC2, and BCL-2 family members as well as certain surface molecules and disease initiating (quiesscent) neoplastic stem cells can be a target for therapies in the future. Potentially, studies will combine the most effective targeted drugs with one another and/or with conventional chemotherapy options to improve patient survival.

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