Leukemia insights

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In this month's Leukemia Insights newsletter, written by Hussein A. Abbas, M.D., Ph.D., Lucia Masarova, M.D., Naveen Pemmaraju, M.D., and Prithviraj Bose, M.D., we focus on two rare myeloid diseases—systemic mastocytosis (SM) and hypereosinophilic syndrome (HES)—that impact mast cells and eosinophils, respectively, and can cause a significant symptom burden for patients. Accurate diagnosing these conditions is often challenging due to the relapsing and remitting nature of some symptoms and the nonspecific manifestations, which can lead to delays in effective management. Learn more about our Leukemia program.

Rare myeloid disorders: Systemic mastocytosis and hypereosinophilia

Systemic mastocytosis (SM):

An overview

Systemic mastocytosis (SM) is a rare mast cell neoplasm characterized by abnormal proliferation, tissue infiltration, and dysfunction, affecting the bone marrow and/or extracutaneous tissues. Approximately 95% of patients with SM have an activating point mutation in the c-KIT gene (D816V).

Symptoms and diagnosis

Patients with SM often experience chronic congestion, diarrhea, brain fog, headaches, fatigue, weight loss, skin eruptions, osteoporosis, recurrent fainting episodes, and heightened allergic reactions to insect stings from bees, wasps, and fire ants. Many of these symptoms are also present in other conditions, making SM challenging to diagnose. A blood test measuring tryptase, an enzyme produced by mast cells, often serves as an initial indicator of SM if elevated. However, elevated tryptase levels can also be seen in hereditary alpha tryptasemia (HAT), a condition affecting up to 5% of the population. Due to the complexities in diagnosing SM, evaluation and management should ideally be conducted at specialized centers.

Confirming and diagnosis

A definitive diagnosis of systemic mastocytosis requires a bone marrow biopsy along with additional tests to evaluate tryptase levels, evaluate KIT mutations, and assess abnormal mast cell markers using flow cytometry or immunohistochemistry. Once SM is confirmed, further testing is done to determine the specific SM subtype.

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Systemic mastocytosis is categorized into six main subtypes:

- Indolent SM (iSM)
- Bone Marrow Mastocytosis (BMM)
- Smoldering SM (SSM)
- Aggressive SM (ASM)
- Mast Cell Leukemia (MCL)
- SM with Associated Hematologic Neoplasm (SM-AHN)

ISM, BMM and SSM are considered non-advanced SM, while ASM, MCL and SM-AHN are generally considered advanced SM.

Patients are classified into these subtypes based on the presence and number of "B" findings (e.g., presence of >30% mast cells in bone marrow, serum tryptase >200 ng/mL, bone marrow changes not meeting formal criteria for MDS or MPN, hepatomegaly without liver dysfunction, splenomegaly without hypersplenism, and KIT allelic frequency >10%) and "C" findings (e.g., bone marrow dysfunction causing cytopenias, hypersplenism, lytic skeletal lesions larger than 2 cm, liver dysfunction, or malabsorption causing weight loss).

Treatment approaches

Treatment strategies for SM differ based on the disease's classification as non-advanced or advanced, with approaches tailored to each patient's unique needs.

In non-advanced SM, treatment focuses on managing symptoms and avoiding known triggers. Anti-mediator medications, including antihistamines, mast cell stabilizers, neuromodulators, and short courses of corticosteroids are commonly used. For refractory cases, the KIT D816V inhibitor avapritinib is approved for symptomatic indolent SM (iSM), aiming to improve quality of life while minimizing side effects. For refractory cases, cytoreductive therapies such as cladribine may be considered, albeit rarely. **In advanced SM subtypes**, treatment involves symptomatic management similar to that in non-advanced SM, along with tyrosine kinase inhibitors (e.g. midostaurin, avapritinib or imatinib) to end-organ damage. Allogeneic stem cell transplantation should be considered for these patients based on risk profile. Notably, imatinib is not effective in the presence of KIT D816V, reducing its role to a minority of patients (<5%).

All patients with SM should carry at least two EpiPens to prevent life-threatening anaphylactic reactions. Occasionally, steroids can be used to control flare-ups. All SM patients should be evaluated in coordination with dermatologists, allergists or immunologists, and/or gastroenterologists depending on symptom spectrum.

Clinical trials

Given the debility of the disease, and the limited efficacy of the approved treatments, enrolling patients on clinical trials to help improve the treatment landscape is critical. At MD Anderson Cancer Center, we currently have three clinical trials for advanced or non-advanced SM.

APEX study: This is a Phase 2, open-label, 2-part clinical study to evaluate the safety, efficacy, pharmacokinetics, pharmacodynamics of bezuclastinib (a KIT inhibitor) in adult patients with advanced SM (ASM, SM-AHN or MCL). Bezuclastinib is a highly selective and potent mutant KIT (D816V) inhibitor that exhibits limited brain penetration, spares off-target kinases and has demonstrated exciting results in the indolent form of the disease (SUMMIT) trial. This study is actively recruiting patients.

HARBOR study: This is a phase 2/3, randomized, double-blind, placebo-controlled study of elenestinib (KIT inhibitor that only minimally crosses the blood brain barrier) in ISM. Part 1 of this study is complete. Part 2 is expected to be open and start to recruit patients in early 2025.

TL-895 study: This is a phase 1/2 study of TL-895 (BTK inhibitor) in ISM. This novel approach aims at targeting BTK instead of KIT, which is a pathway that is activated in SM and may underlie many of the symptoms of the disease. This study is actively recruiting patients.

Hypereosinophilia:

An overview

Hypereosinophilia is a rare disorder, typically diagnosed by detecting elevated eosinophil levels (≥1500/microL) in the peripheral blood on two separate occasions at least one month apart, and/or through the pathologic identification of eosinophilic infiltration in tissues. Hypereosinophilia is often discovered incidentally during routine testing or in the evaluation of recurrent allergies, gastrointestinal ulcers, or skin rashes. When hypereosinophilia is associated with organ damage, it is classified as hypereosinophilic syndrome (HES).

Diagnosis

Diagnostic work-up of HES is complex and first requires ruling out secondary causes (reactive often resulting from parasitic infections, certain solid tumors or the lymphocytic subvariant). In absence of a secondary cause, screening for a clonal disorder should ensue and includes screening for FIP1L1::PDGFRA, or other reciprocal translocations involving PDGFRA (4q12), PDGFRB (5q31-q33), FGFR1 (8p11), JAK2 (9p24), FLT3 (13q12) or ETV6::ABL1. Of note, many of these changes cannot be detected by conventional cytogenetics and would require additional studies such as FISH or Optical Genome Mapping. If any of these abnormalities are detected, then a myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions is likely diagnosis. In absence of these clonal abnormalities, the diagnosis could be related to T-cell lymphocytic variants or idiopathic HES.

Based on the diagnostic work-up, HES can fall into any of these categories:

- **Primary (neoplastic/clonal) HES** – A bone marrow disorder arising from the clonal expansion of eosinophils, possibly due to an underlying eosinophilic neoplasm.

- **Secondary (reactive) HES** – Typically polyclonal in nature, it often resulting from parasitic infections or certain tumors, such as lymphomas

- **Idiopathic HES** – When a definitive cause cannot be identified. When diagnosing iHES, it is essential to rule out other potential conditions, such as eosinophilic granulomatosis with polyangiitis (EGPA).

Treatment

The primary goals in treating HES are to control symptoms and prevent end-organ damage. In rare cases, HES requires urgent cytoreductive therapy, particularly if patients are at risk of acute events, such as stroke or cardiac complications, due to elevated eosinophil levels. This scenario usually arises in primary (neoplastic) HES, a clonal disorder that is often, but not always, associated with the FIP1L1::PDGFRA fusion, which is highly responsive to imatinib. Pemigatinib (inhibitor of FGFR1-3) is approved in the FGFR1-rearranged subtype. In cases where a clonal

abnormality cannot be confirmed, high-dose steroids may be administered to manage acute symptoms attributed to HES. For Idiopathic HES, symptom-directed therapies are used, including a trial of steroids. Mepolizumab, an anti-IL5 agent, is a treatment option, especially for patients who do not respond adequately to steroids. More recently benralizumab (anti-IL5 receptor antibody) has been investigated.

For any questions about SM or hypereosinophilia, contact Hussein Abbas, M.D., Ph.D. at habbas@mdanderson.org.