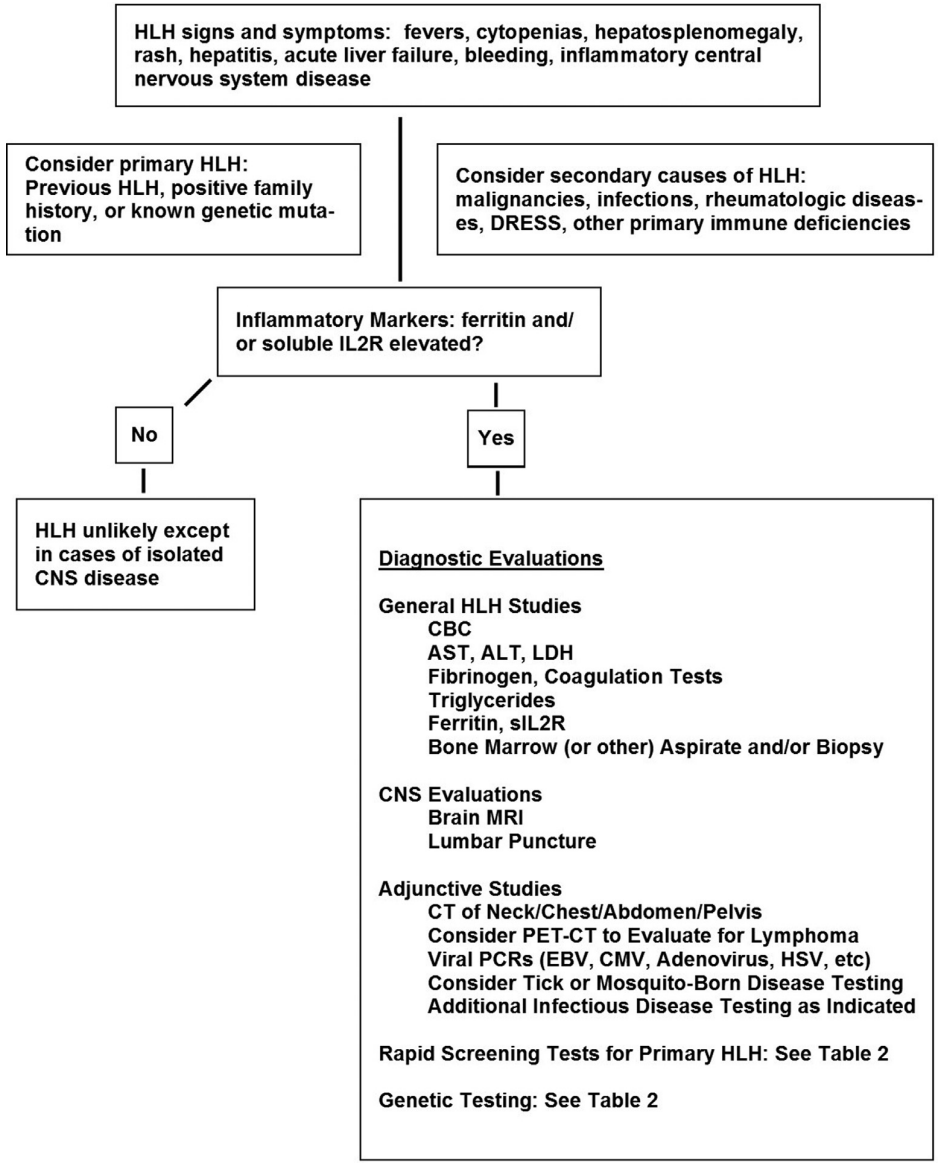
# Bone Marrow Disorders

# Hemophagocytic Lymphohistiocytosis (HLH): Pathophysiology

- Hemophagocytic lymphohistiocytosis (HLH) is an overwhelming clinical syndrome associated with extreme immune activation.
- Activated lymphocytes and macrophages infiltrate organs causing secondary clinical manifestations.
  - Bone marrow (cytopenias, fevers); liver (hepatic dysfunction); skin (rash); lymph nodes (lymphadenopathy); spleen (splenomegaly); central nervous system (seizures and/or focal deficits to encephalopathy)
- HLH is life-threatening due to rapid progression to multisystem organ failure if the diagnosis is not considered and immunosuppression confidently initiated.
- Primary HLH is a genetic disease found in children.
  - Primary HLH is almost universally fatal without treatment.
- Secondary HLH is associated with various underlying immunodeficiency, autoimmune, infections or malignant disorders and is more common in adults.
  - Case series of adults treated with a variety of regimens report a 30-day mortality of 20% to 44% and overall mortality of 50% to 75%.
  - Patients with HLH associated with malignancy suffer a worse prognosis.

Risma KA, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):824-832; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

# Suggested Diagnostic Strategy for the Syndrome of HLH




ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell count; CNS = central nervous system; CMV = cytomegalovirus; CT = computed tomography; EBV = Epstein-Barr virus; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; HSV = herpes simplex virus; LDL = lactate dehydrogenase; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; sILR2 = soluble IL-2 receptor.

Risma KA, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):824-832.

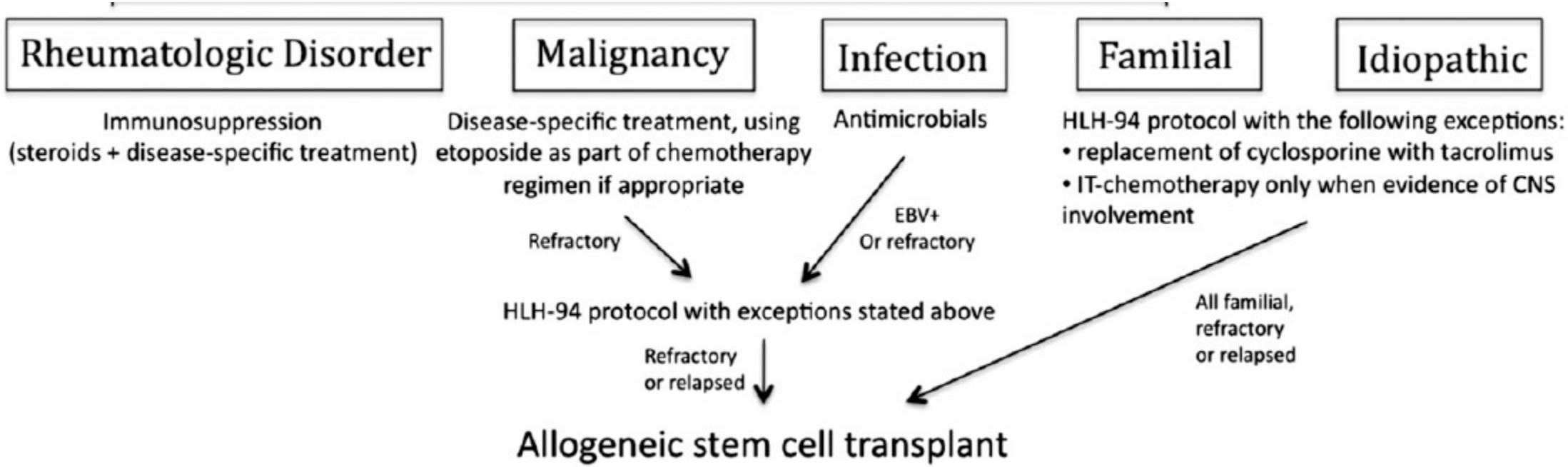
# HLH: Diagnostic Guidelines for HLH

Diagnosis of HLH requires a molecular diagnosis consistent with HLH or 5 of 8 of the following criteria:

1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥ 2 lineages
    a. Hemoglobin < 9 g/dL
    b. Platelets < $100 \times 10^9$/L
    c. Neutrophils < $1.0 \times 10^9$/L
4. Hypertriglyceridemia and/or hypofibrinogenemia
    a. Triglycerides ≥ 265 mg/dL
    b. Fibrinogen ≤150 mg/dL
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK cell activity
7. Ferritin ≥ 500 mg/L
8. sCD25 (ie, sIL2R) ≥ 2400 U/mL

Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

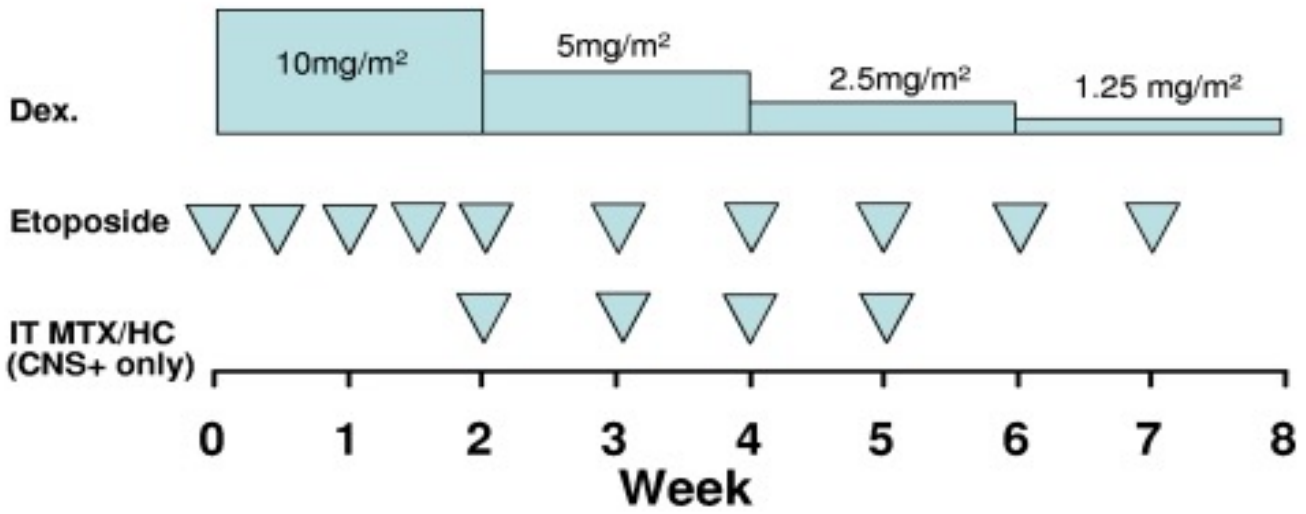
# HLH: Clinical Management




CNS = central nervous system; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis; IT = immunotherapy

Jordan MB, et al. *Blood*. 2011;118:4041-4052; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

# HLH-94 Protocol




## Induction therapy for HLH in adults

- Etoposide is dosed as 150 mg/m$^2$ per dose
- Dexamethasone (Dex.) is dosed as indicated and may be given orally or intravenously, although the latter is preferred at therapy initiation
- Intrathecal methotrexate and hydrocortisone (IT MTX/HC) should be given to patients with evidence of CNS involvement, as early as LP may be safely performed (which may vary from the diagram) and dosed > 3 years, 12/15 mg
- Weekly intrathecal therapy is generally continued until at least 1 week after resolution of CNS involvement (both clinical and CSF indices)

CNS = central nervous system; CSF = cerebrospinal fluid; LP = lumbar puncture

Jordan MB, et al. *Blood*. 2011;118:4041-4052; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

# HLH Resources

- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/hemophagocytic-lymphohistiocytosis/

# Castleman's Disease: Epidemiology and Pathophysiology

- Castleman disease(s) (CD) represent lymphoproliferative disorders
  - Encompasses several distinct clinicopathological disorders at the intersection of hematology, immunology, oncology, rheumatology, and virology
  - Have a wide range of etiologies, presentations, treatments, and outcomes
- Unicentric CD (UCD): One single lymph node station
  - Likely a clonal neoplastic process
  - Most likely cell of origin is stromal, specifically the follicular dendritic cell
- Clinically multicentric CD (MCD): Disseminated disease
  - POEMS-MCD: polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD
  - Idiopathic MCD (iMCD)
    - iMCD-TAFRO: thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly
    - iMCD-NOS: iMCD not otherwise specified
  - Human herpesvirus-8–associated MCD (HHV-8+ MCD)
    - Uncontrolled HHV8 infection is the etiological driver in HHV8-MCD

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

# Clinical Features of Castleman's Disease

| Feature | UCD | iMCD-NOS | iMCD-TAFRO | POEMS-Associated MCD | HHV-8+-MCD |
|---|---|---|---|---|---|
| Age | Fourth decade | Fifth to sixth decade | Fifth decade | Fifth decade | Fifth decade HIV positive; seventh decade HIV negative |
| Systemic symptoms | ± | ++<br>Occasional PN | +++<br>Anasarca | ++ | +++<br>Kaposi sarcoma |
| Lymphadenopathy | Central most common; often bulky | Peripheral plus central; often small volume | Peripheral plus central; often small volume | Peripheral plus central | Peripheral plus central; often small volume |
| Organomegaly | ± | ++ | +++ | +++ | +++ |
| Abnormal inflammatory markers | ± | ++ | +++<br>Increased prolactin | ++ | +++ |
| Anemia, thrombocytopenia, abnormal LFTs | ± | ++<br>Sometimes thrombocytosis | +++ | ± | +++<br>HHV8 DNA detectable in plasma |

+ sometimes present; ++ often present; +++ very often present; - rarely present

HHV8 = human herpesvirus-8; HIV = human immunodeficiency virus; iMCD = idiopathic MCD; LFTs = liver function tests; MCD = multicentric disease; NOS = not otherwise specified; PN = peripheral neuropathy; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TAFRO = thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly; UCD = unicentric disease

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

# Clinical Features of Castleman's Disease (cont)

| Feature | UCD | iMCD-NOS | iMCD-TAFRO | POEMS-Associated MCD | HHV-8+-MCD |
|---|---|---|---|---|---|
| Hypergammaglobulin-emia | ± | +++ | ± | + | +++ |
| Renal dysfunction | - | + | ++<br>Invasive coagulation and fibrinolysis | + | ++ |
| Autoimmune phenomena | Rare, but PNP can be seen | ++<br>AIHA, PNP, ITP, ILD | ± | ± | Positive DAT in 46%, MG in 28% |
| Pathological features | Usually, HV variant | Usually, PC variant | Usually mixed or hypervascular | Usually mixed or PC type | Usually, PC variant and often plasmablastic |

+ sometimes present; ++ often present; +++ very often present; - rarely present

AIHA = autoimmune hemolytic anemia; DAT = direct antiglobulin test; HV = hyaline vascular; ILD = interstitial lung disease; ITP = immune thrombocytopenic purpura; MG = monoclonal gammopathy; PNP = paraneoplastic pemphi; PC = plasma cell

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

# Clinical Features of Castleman's Disease (cont)

| Feature | UCD | iMCD-NOS | iMCD-TAFRO | POEMS-Associated MCD | HHV-8+-MCD |
|---|---|---|---|---|---|
| Therapy | Surgery | IL-6 targeted therapy, rituximab, systemic therapies | Same as iMCD but also calcineurin inhibitors | Local radiation Myeloma type therapy, including ASCT | Rituximab, etoposide |
| Clinical course | Benign | Variable | Very Aggressive | Aggressive | Aggressive |
| Risk for lymphoma | + | + | ± | ± | ++ |

+, sometimes present; ++, often present; +++, very often present; -, rarely present;
ASCT = autologous stem cell transplant
*Fever, sweats, weight loss, malaise, effusions, autoimmune, and respiratory symptoms

Dispenzieri A, et al. Blood. 2020;135(16):1353-1364.

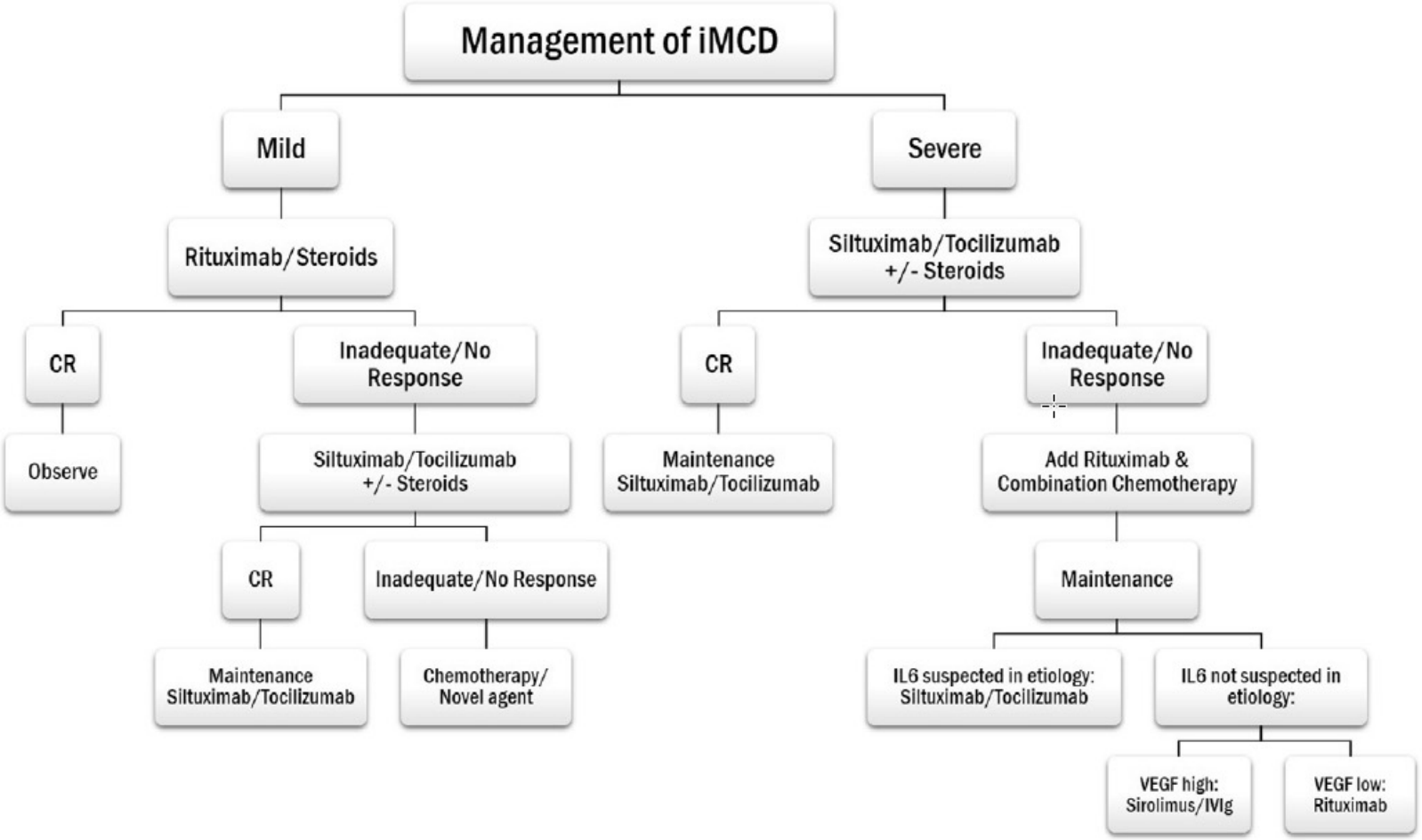
# Treatment Options for Castleman's Disease

| iMCD-NOS and iMCD-TAFRO | POEMS-Associated | HHV-8+-MCD |
|---|---|---|
| **First-Line Therapy** | | |
| • Siltuximab<br>• Tocilizumab<br>• Corticosteroids | • If no bone lesions, iMCD-like therapy<br>• If bone lesions, myeloma type therapy including ASCT | • If HIV-positive, combination antiretroviral therapy<br>• Rituximab |
| **Second-Line and Beyond Options** | | |
| • Rituximab<br>• Cyclosporin<br>• Sirolimus<br>• IVIG<br>• Thalidomide<br>• Lenalidomide<br>• Bortezomib<br>• R-CVP, R-CHOP<br>• ASCT†<br><br>†Increased ESR, CRP, cholinesterase, ferritin, and low albumin | • As above | • Etoposide<br>• Liposomal doxorubicin<br>• Interferon<br>• Antiviral therapy |

ASCT = autologous stem cell transplant; HIV = human immunodeficiency virus; IVIG = intravenous immunoglobulin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Dispenzieri A, et al. Blood. 2020;135(16):1353-1364

# Management of iMCD



# Castleman's Disease: Clinical Resources

- All patients with a diagnosis of CD should be encouraged to register for the Castleman Disease Collaborative Network (CDCN) ACCELERATE natural history registry (#NCT02817997, www.CDCN.org/ACCELERATE ) and be informed of opportunities to contribute blood samples to research (www.CDCN.org/samples )
- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/castlemans-disease/

# Mastocytosis: Pathophysiology

- Mastocytosis comprises a heterogeneous group of disorders characterized by expansion and accumulation of neoplastic mast cells in 1 or more organ systems.
- Subvariants of mastocytosis include
  - Cutaneous mastocytosis (CM), in which no systemic involvement is found
  - Systemic variants (SM)
    - SM may be aggressive (ASM) or more indolent (ISM)
- Organ involvement may include
  - Spleen, liver, gastrointestinal tract
  - Bone marrow is involved in virtually all patients regardless of the type of SM
  - Skin involvement is usually found in patients with indolent SM (ISM)
- More than 90% of patients with systemic mastocytosis (SM) have a gain-of-function mutation in codon 816 of the receptor tyrosine kinase (*KIT* D816V)

Valent P, et al. Blood 2017;129(11):1420-1427.

# Symptoms of Other Illnesses Mimicking Systemic Mastocytosis

- **Inflammatory bowel disease:** Patients may experience weight loss, abdominal cramping and pain, nausea and vomiting, fatigue, and irregular bowel movements
- **Irritable bowel syndrome:** Patients may experience heartburn, nausea and vomiting, presence of clear or white mucus, abdominal pain, and presence of constipation or diarrhea
- **Malabsorption:** Patients may experience diarrhea and weight loss; however, more characteristic symptoms are often based on the specific cause
- **Myeloproliferative neoplasms:** Patients can experience fatigue, weight loss, abdominal discomfort, easy bruising or bleeding, infections, and other symptoms.
- **Other symptoms:** Urticaria, flushing

# Systemic Mastocytosis: Diagnostic Criteria

| | |
|---|---|
| **Major Systemic Mastocytosis (SM) Criterion** | Multifocal dense infiltrates of MCs (≥ 15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s) |
| **Minor SM Criterion** | a. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs |
| | b. KIT point mutation at codon 816 in the BM or another extracutaneous organ |
| | c. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 |
| | d. Baseline serum tryptase level > 20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion) |
| *If at least 1 major SM criterion and 1 minor SM criterion or 3 minor SM criteria are fulfilled, the diagnosis of SM can be established* | |

# Mastocytosis: Clinical Management

- Currently, there is no curative treatment for mastocytosis
- Treatment of mastocytosis is primarily directed at controlling the symptoms caused by the release of mast cell mediators
  - H1 and H2 antihistamines are therefore cornerstones of the treatment to relieve symptoms
  - Cromolyn sodium can be especially effective for the treatment of some gastrointestinal symptoms, decreasing bone pain, treating headaches and some of the skin manifestations.
  - Mast-cell stabilizers such as ketotifen can be used to treat some of the skin involvement
  - Leukotriene antagonists can also be used to improve symptoms in patients
  - Proton-pump inhibitors can be used to treat the increased acid production in the stomach
  - Steroids may be necessary in patients unresponsive to other therapy or with more advanced disease

# Mastocytosis: Clinical Management (cont)

- *KIT* D816V, a primary oncogenic driver of MC differentiation, proliferation, and survival, is an attractive target because of its high frequency in systemic mastocytosis (SM)
  - In 2017, midostaurin (Rydapt) was approved by the FDA for the treatment of adults with aggressive SM, with SM with associated hematological neoplasm, or with mast cell leukemia
  - National Comprehensive Cancer Network guidelines are now available to guide treatment approaches to SM, including the use of midostaurin and enrollment in clinical trials using KIT inhibitors or other agents
  - Allogeneic stem cell transplantation remains a preferred option for eligible patients with SM

# Mastocytosis: Clinical Resources

- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/mastocytosis/
- The Mast Cell Disease Society, Inc.
  http://www.tmsforacure.org/