National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Castleman Disease

Version 1.2025 — December 19, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2025 of the NCCN Guidelines for Castleman Disease from Version 1.2024 include:

Global changes

- All regimens and corresponding footnotes in algorithm pages moved to new Suggested Treatment Regimen pages (CD-C).
- Statement, "An FDA-approved biosimilar is an appropriate substitute for rituximab" replaced by the general footnote: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- References for suggested treatment regimens were updated throughout the guidelines.

CD-1

- Diagnosis
  - 1st bullet revised: Excisional or incisional biopsy *is preferred for the definitive diagnosis.*
  - 2nd bullet revised: A fine-needle aspiration (FNA) biopsy ~~alone is not generally suitable~~ *is insufficient* for the initial diagnosis *or histologic assessment of* Castleman disease (CD). A core needle biopsy is not optimal ~~but can be used under certain circumstances~~ *because features of CD are very nonspecific and seeing the whole node with architecture is essential to be confident of the diagnosis. Therefore, core needle biopsy is unlikely to be adequate for definitive pathologic diagnosis of CD.* ~~but can be used under certain circumstances. Core needle biopsy (multiple biopsies preferred) is an appropriate alternative to excisional or incisional biopsy, especially in certain circumstances (when a lymph node is not easily accessible for excisional or incisional biopsy or if surgical biopsy would cause significant morbidity or substantial treatment delays); a combination of core needle biopsy (multiple biopsies preferred) and FNA biopsies biopsy in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry [IHC], flow cytometry, molecular analysis to detect immunoglobulin [Ig] gene rearrangements, karyotype or fluorescence in situ hybridization [FISH] for major translocationsa) may be sufficient for diagnosis.~~
  - 3rd bullet revised: Hematopathology review of all slides with at least one paraffin block representative of the ~~tumor~~ *lesion*. Rebiopsy if consult material is nondiagnostic, *preferably the most FDG-avid, accessible lymph node*.
  - Bullet removed: Histologic grading cannot be performed on an FNA.
- Additional diagnostic testing
  - IHC: CD5, CD138 moved from Essential to Useful.
  - EBER-ISH moved from Essential to Useful.
  - Useful, 1st bullet: TCR removed.
- Footnote d revised: There are 3 variants: hypervascular (hyaline vascular), plasmacytic, and mixed variants. Hypervascular variant is virtually always unicentric and human herpesvirus 8 (HHV8) (-). Plasmacytic and mixed variants are *more often* multicentric and *may be* HHV8+.

CD-2

- Workup
  - Hepatitis C testing moved from Useful to Essential and corresponding footnote added: Hepatitis C antibody and if positive, viral load and consult with hepatologist.
  - Footnote e revised by adding: Patients with POEMS-associated MCD should have treatment directed at POEMS syndrome with regimens recommended for the treatment of multiple myeloma (see NCCN Guidelines for Multiple Myeloma).

CD-4

- MCD
  - New pathway added: Fulminant/Severe HHV8(+) MCD ± organ failure or Fulminant/Severe HHV8(-)-iMCD
- Footnote o added: Severe disease defined as: Eastern Cooperative Oncology Group (ECOG) performance status ≥2; stage IV kidney dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2, creatinine >3 mg/dL); anasarca and/or ascites, pleural effusion, or pericardial effusion; hemoglobin ≤8 g/dL; pulmonary involvement/ interstitial pneumonitis with dyspnea (van Rhee F, et al. Blood 2018;132:2115-2124). (Also for CD-5)
- Footnote r revised: Occult KS is prevalent in HIV/HHV8+ MCD and *is likely to* ~~may~~ flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± gastrointestinal (GI) *involvement* ~~in patients receiving concurrent KS-directed therapy (ie, addition of liposomal doxorubicin)~~. *Monitor closely for KS progression and continue KS-directed therapy for ~3 months post last rituximab to minimize risk of KS flare (given long action of rituximab).* See NCCN Guidelines for Kaposi Sarcoma. (Also for CD-5 and CD-6)

Continued

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Updates in Version 1.2025 of the NCCN Guidelines for Castleman Disease from Version 1.2024 include:

CD-5
- Fulminant/Severe HHV8(+) MCD ± organ failure or Fulminant/Severe HHV8(-)-iMCD
  - Added new pathway for first-line therapy and relapsed disease

CD-6
- Algorithm clarified: *RELAPSED*/REFRACTORY OR PROGRESSIVE DISEASE *(MCD)*
- Algorithm separated by:
  - HHV8(+) - Criteria for active disease present with no organ failure or Fulminant/severe [HHV8(+) or HHV8(-)] disease with no organ failure
  - Fulminant/severe [HHV8(+) or HHV8(-)] disease with organ failure
- After no response revised: ~~Treat with~~ Alternate *second-line* combination therapy ± rituximab *(CD-C 2 of 3)* not previously given *before moving onto subsequent therapy*
- After relapsed/refractory disease
  - HDT/ASCR removed.

CD-C 1 of 3
- Suggested treatment regimens, First-line therapy
  - MCD - Criteria for active disease present but no organ failure
    - ◊ HHV8-negative/HIV-1-negative (iMCD - Nonsevere)
      - R-CVP added.
      - Removed preference stratification
  - MCD - Fulminant/severe ± organ failure
    - ◊ Fulminant/severe HHV8-negative (iMCD), regimens added:
      - CHOP ± rituximab
      - CVAD ± rituximab
      - CVP ± rituximab
      - Siltuximab
      - If not a candidate for combination therapy: Rituximab
    - ◊ Fulminant/severe HHV8-positive MCD, regimens added:
      - Rituximab + liposomal doxorubicin
      - Rituximab + prednisone + liposomal doxorubicin

CD-C 2 of 3
- Suggested treatment regimens, Second-line and subsequent therapy for relapsed/refractory or progressive disease
  - HHV8(+) - Criteria for active disease present with no organ failure or Fulminant/Severe disease [HHV8(+) or HHV8(-)] with no organ failure
    - ◊ Preferred regimens, added: Siltuximab (if HHV8-negative)
    - ◊ Other recommended, added: Sirolimus
  - Fulminant/Severe disease [HHV8(+) or HHV8(-)] with organ failure
    - ◊ Preferred regimens, added: Siltuximab (if HHV8-negative)
  - Liposomal doxorubicin, liposomal doxorubicin ± rituximab, and high-dose zidovudine + valganciclovir clarified as "if HHV8-positive."

DIAGNOSIS

- **Excisional or incisional biopsy is preferred for the definitive diagnosis.**
- **A fine-needle aspiration (FNA) biopsy is insufficient for the initial diagnosis or histologic assessment of Castleman disease (CD). A core needle biopsy is not optimal because features of CD are very nonspecific and seeing the whole node with architecture is essential to be confident of the diagnosis. Therefore, core needle biopsy is unlikely to be adequate for definitive pathologic diagnosis of CD.**
- **Hematopathology review of all slides with at least one paraffin block representative of the lesion. Rebiopsy if consult material is nondiagnostic, preferably the most fluorodeoxyglucose (FDG)-avid, accessible lymph node.**

→

ADDITIONAL DIAGNOSTIC TESTING[a,b,c]

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis**
  - **IHC panel: kappa/lambda, CD20, CD3, HHV8 latency-associated nuclear antigen (LANA)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect immunoglobulin (Ig) gene rearrangements**
- **IHC panel: Ki-67 index; Ig heavy chains,[d] CD5, CD10, BCL2, BCL6, cyclin D1, CD21, or CD23, CD38, IRF4/MUM1, PAX5, CD138**
- **Flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10**
- **Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH)**

→ **Workup (CD-2)**

[a] If a high suspicion of a clonal process remains and other techniques have not resulted in a clear identification of a clonal process, then next-generation sequencing (NGS) can be used.
[b] For HIV-related lymphomas associated with CD, see NCCN Guidelines for B-Cell Lymphomas - HIVLYM. For diffuse large B-cell lymphoma (DLBCL)-associated with CD in patients without HIV infection, see NCCN Guidelines for B-Cell Lymphomas - DLBCL.
[c] There are 3 variants: hypervascular (hyaline vascular), plasmacytic, and mixed variants. Hypervascular variant is virtually always unicentric and human herpesvirus 8 (HHV8) (-). Plasmacytic and mixed variants are more often multicentric and may be HHV8+.
[d] In HHV8+ plasmacytic variant, plasmablasts are IgM lambda while normal plasma cells are IgG or IgA polytypic.

Note: All recommendations are category 2A unless otherwise indicated.

WORKUP[e]

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- Assess for criteria for active disease[f]
- Complete blood count (CBC) with differential
- Comprehensive metabolic panel
- LDH, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)
- Beta-2-microglobulin, SPEP and urine electrophoresis with immunofixation, serum light chains, quantitative Ig
- HIV, HHV8, hepatitis B testing,[g] hepatitis C testing,[h] EBV PCR
- PET/CT scan (preferred) or C/A/P CT with contrast of diagnostic quality
- Pregnancy testing in patients of childbearing age (if chemotherapy or radiation therapy [RT] planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- If HHV8 or HIV positive, screening for concurrent Kaposi sarcoma (KS) is strongly recommended
- Bone marrow biopsy + aspirate
- Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
- Neck CT with contrast
- Echocardiogram or multigated acquisition (MUGA) scan if anthracycline-based regimen is indicated
- IgG4, sIL6, sIL10, vascular endothelial growth factor receptor (VEGF), uric acid, ferritin[i]
- Discuss fertility preservation[j]

CASTLEMAN DISEASE SUBTYPE

- Unicentric Castleman disease (UCD) → CD-3
- Multicentric Castleman disease (MCD) → CD-4

[e] See Subtypes of Idiopathic MCD (CD-A). Rule out other diseases that can mimic idiopathic MCD (iMCD) (see Exclusion Criteria on CD-B 1 of 2). If concurrent polyneuropathy and monoclonal plasma cell disorder, a workup for polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome is recommended. Patients with POEMS-associated MCD should have treatment directed at POEMS syndrome with regimens recommended for the treatment of multiple myeloma (see NCCN Guidelines for Multiple Myeloma).

[f] Criteria for Active Disease (CD-A).

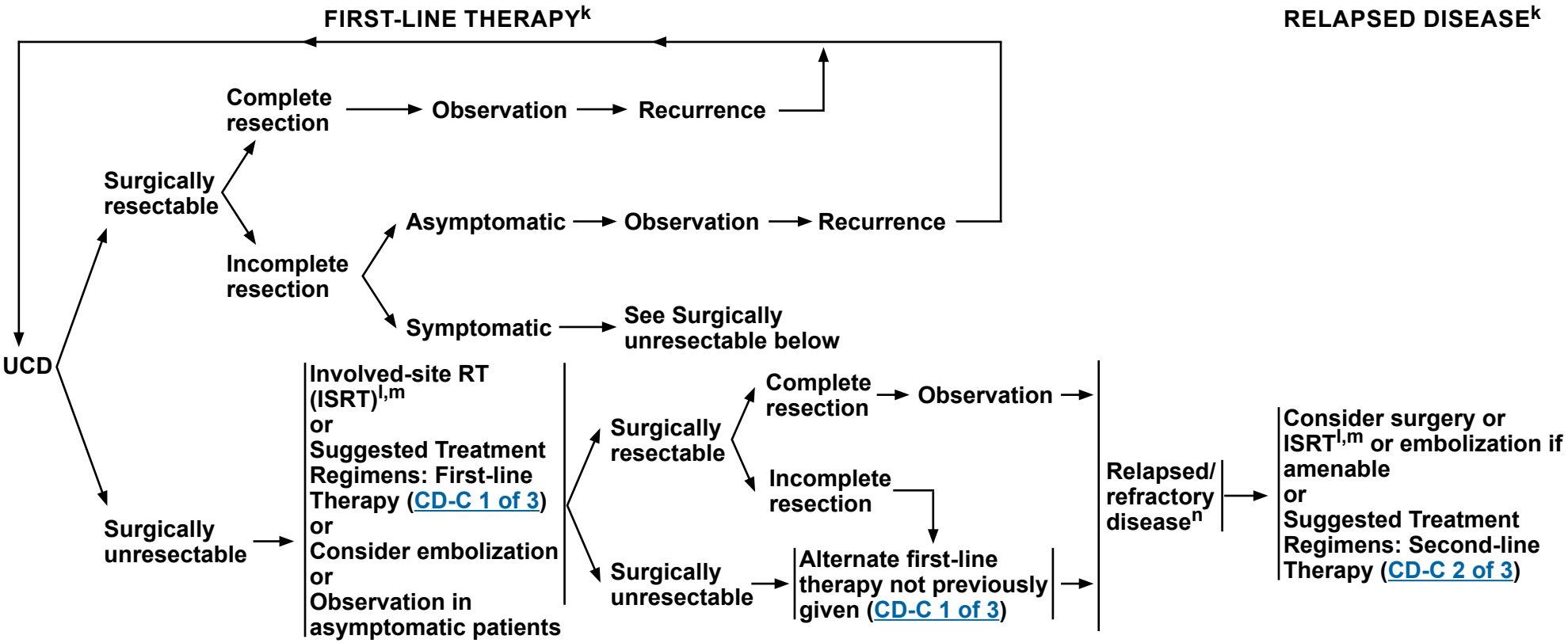
[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. See Monoclonal Antibody Therapy and Viral Reactivation (NHODG-B) in the NCCN Guidelines B-Cell Lymphomas. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consider consult with gastroenterologist.

[h] Hepatitis C antibody and if positive, viral load and consult with hepatologist.

[i] Measurement of acute phase reactants may be helpful in monitoring therapy.

[j] Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

Note: All recommendations are category 2A unless otherwise indicated.



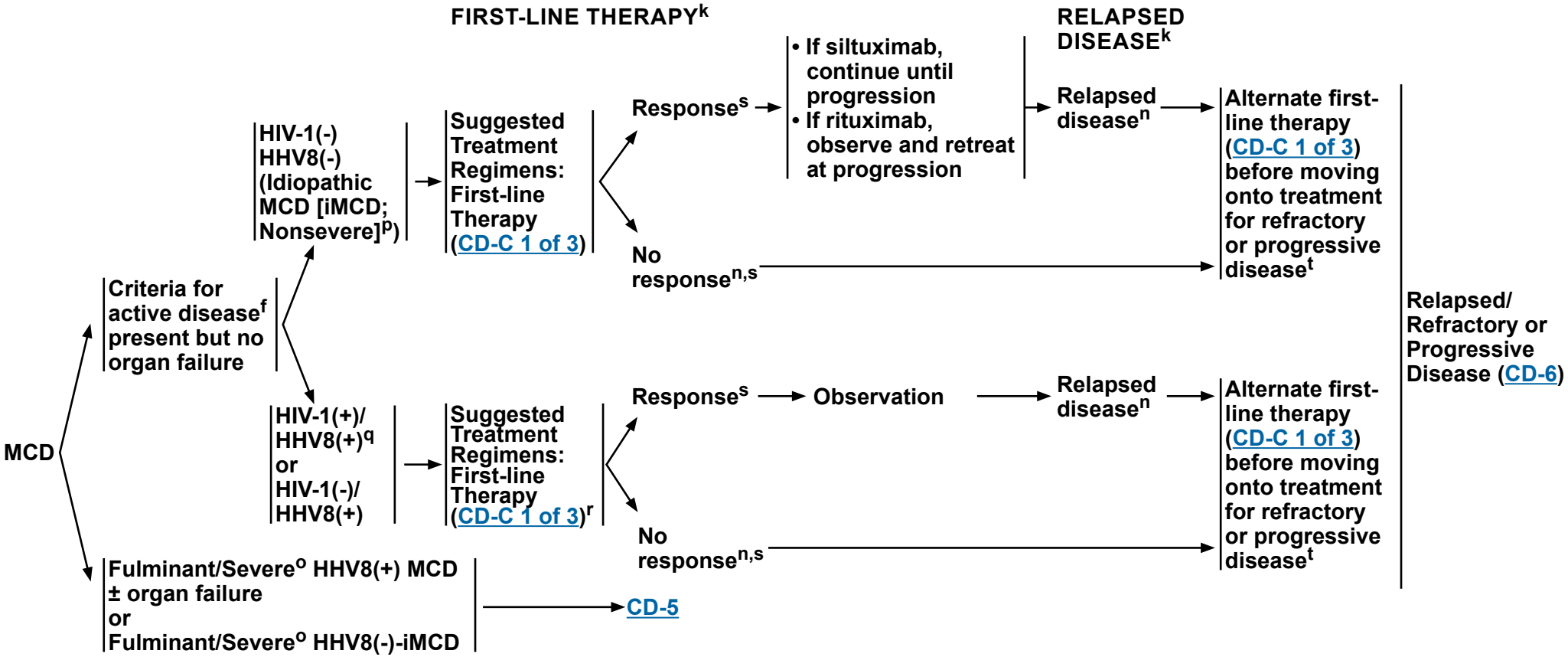
[k] See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the NCCN Guidelines for B-Cell Lymphomas.

[l] The optimal dose of ISRT in unresectable UCD is not established. Doses as high as 40 Gy in 1.5–2 Gy fractions have been used (Chronowski GM, et al. Cancer 2001;92:670-676). Lower doses may be considered depending upon clinical circumstances (eg, proximity to critical structures, treatment intent). Advanced radiation techniques (eg, intensity-modulated RT [IMRT], image-guided RT [IGRT], protons) are recommended to limit dose to surrounding normal tissues (Matthiesen C, et al. Radiol Oncol 2012;46:265-270). RT Dose Constraint Guidelines for Lymphoma - Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy section of the NCCN Guidelines for Hodgkin Lymphoma.

[m] Patients with non-bulky disease may be observed after ISRT.

[n] Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Note: All recommendations are category 2A unless otherwise indicated.



[f] Criteria for Active Disease (CD-A).

[k] See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the NCCN Guidelines for B-Cell Lymphomas.

[n] Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

[o] Severe disease defined as: Eastern Cooperative Oncology Group (ECOG) performance status ≥2; stage IV kidney dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2, creatinine >3 mg/dL); anasarca and/or ascites, pleural effusion, or pericardial effusion; hemoglobin ≤8 g/dL; pulmonary involvement/interstitial pneumonitis with dyspnea (van Rhee F, et al. Blood 2018;132:2115-2124).

[p] Diagnostic Criteria for Idiopathic MCD (CD-B).

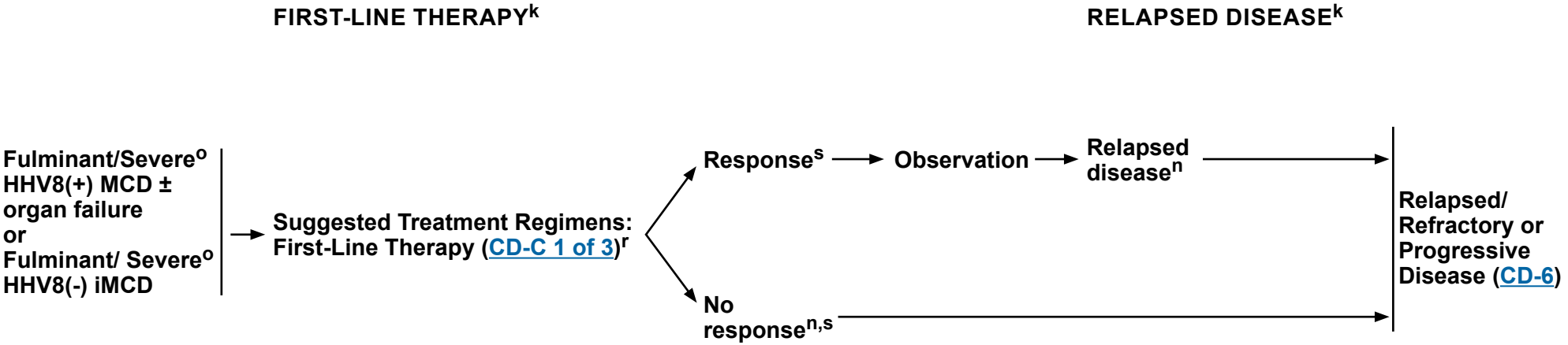
[q] All patients with HIV infection should be on combination antiretroviral therapy (cART). For principles of concurrent HIV management and supportive care, see the NCCN Guidelines for Cancer in People with HIV.

[r] Occult KS is prevalent in HIV/HHV8+ MCD and is likely to flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± gastrointestinal (GI) involvement. Monitor closely for KS progression and continue KS-directed therapy for ~3 months post last rituximab to minimize risk of KS flare (given long action of rituximab). See NCCN Guidelines for Kaposi Sarcoma.

[s] Response assessment using the imaging modalities performed during workup (chest/abdomen/pelvis [C/A/P] CT with contrast or PET/CT).

[t] Rituximab ± prednisone may be repeated without limit if progression ≥6 months after completion of rituximab.

Note: All recommendations are category 2A unless otherwise indicated.



[k] See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the NCCN Guidelines for B-Cell Lymphomas.

[n] Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

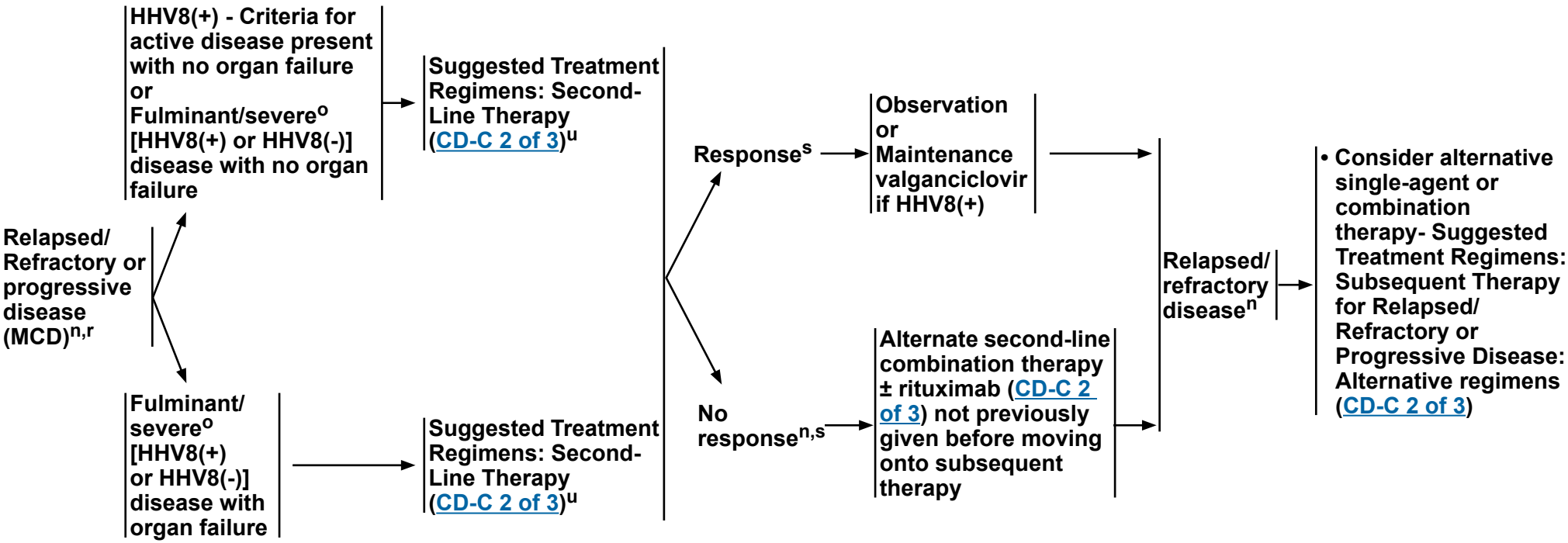
[o] Severe disease defined as: ECOG performance status ≥2; stage IV kidney dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2, creatinine >3 mg/dL); anasarca and/or ascites, pleural effusion, or pericardial effusion; hemoglobin ≤8 g/dL; pulmonary involvement/interstitial pneumonitis with dyspnea (van Rhee F, et al. Blood 2018;132:2115-2124).

[r] Occult KS is prevalent in HIV/HHV8+ MCD and is likely to flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± GI involvement. Monitor closely for KS progression and continue KS-directed therapy for ~3 months post last rituximab to minimize risk of KS flare (given long action of rituximab). See NCCN Guidelines for Kaposi Sarcoma.

[s] Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).

Note: All recommendations are category 2A unless otherwise indicated.

RELAPSED/REFRACTORY OR PROGRESSIVE DISEASE (MCD)[k]



[k] See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the NCCN Guidelines for B-Cell Lymphomas.
[n] Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.
[o] Severe disease defined as: ECOG performance status ≥2; stage IV kidney dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2, creatinine >3 mg/dL); anasarca and/or ascites, pleural effusion, or pericardial effusion; hemoglobin ≤8 g/dL; pulmonary involvement/interstitial pneumonitis with dyspnea (van Rhee F, et al. Blood 2018;132:2115-2124).
[r] Occult KS is prevalent in HIV/HHV8+ MCD and is likely to flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± GI involvement. Monitor closely for KS progression and continue KS-directed therapy for ~3 months post last rituximab to minimize risk of KS flare (given long action of rituximab). See NCCN Guidelines for Kaposi Sarcoma.
[s] Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).
[u] Single-agent therapy is preferred for asymptomatic patients with no organ failure; combination therapy is preferred for patients with fulminant disease and organ failure.

Note: All recommendations are category 2A unless otherwise indicated.

CRITERIA FOR ACTIVE DISEASE[a]

- **Fever**
- **Increased serum C-reactive protein level >20 mg/L in the absence of any other etiology**
- **At least three of the following other MCD-related symptoms:**
  - **Peripheral lymphadenopathy**
  - **Enlarged spleen**
  - **Edema**
  - **Pleural effusion**
  - **Ascites**
  - **Cough**
  - **Nasal obstruction**
  - **Xerostomia**
  - **Rash**
  - **Central neurologic symptoms**
  - **Jaundice**
  - **Autoimmune hemolytic anemia**

[a] Gérard L, Bérezné A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus-associated multicentric Castleman disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25:3350-3356.

SUBTYPES OF IDIOPATHIC MCD[a]

- **Idiopathic MCD (iMCD-TAFRO)**
  - **Marked inflammatory syndrome**
  - **Thrombocytopenia, anasarca, fever/elevated C-reactive protein (CRP), renal dysfunction/reticulin myelofibrosis, organomegaly**
  - **Megakaryocytic hyperplasia, hypervascular or mixed histopathology**
  - **Normal immunoglobulin levels**
- **Idiopathic MCD - not otherwise specified (iMCD-NOS)**
  - **Less intense inflammatory syndrome**
  - **Normal/elevated platelet counts**
  - **Plasmacytic or mixed histopathology**
  - **Polyclonal hypergammaglobulinemia**

[a] Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol 2016;91:220-226.

Note: All recommendations are category 2A unless otherwise indicated.

Consensus Diagnostic Criteria for Idiopathic MCD[a]		
I. Major Criteria (need both):	1. Histopathologic lymph node features consistent with the iMCD spectrum. Features along the iMCD spectrum include (need grade 2–3 for either regressive GCs or plasmacytosis at minimum): - Regressed/atrophic/atretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an "onion skinning" appearance - FDC prominence - Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the GCs with a "lollipop" appearance - Sheetlike, polytypic plasmacytosis in the interfollicular space - Hyperplastic GCs 2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations	
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)	Laboratory* 1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)† 2. Anemia (hemoglobin <12.5 g/dL for males, hemoglobin <11.5 g/dL for females) 3. Thrombocytopenia (platelet count <150 μ/mL) or thrombocytosis (platelet count >400 μ/mL) 4. Hypoalbuminemia (albumin <3.5 g/dL) 5. Renal dysfunction (eGFR <60 mL/min/1.73m^2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL) 6. Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL)	Clinical 1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B-symptoms) 2. Large spleen and/or liver 3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion 4. Eruptive cherry hemangiomatosis or violaceous papules 5. Lymphocytic interstitial pneumonitis
III. Exclusion Criteria (must rule out each of these diseases that can mimic iMCD)	Infection-related disorders 1. HHV-8 (infection can be documented by blood PCR; diagnosis of HHV-8–associated MCD requires positive LANA-1 staining by IHC, which excludes iMCD) 2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary) 3. Inflammation and adenopathy caused by other uncontrolled infections (eg, acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis)	Autoimmune/autoinflammatory diseases (requires full clinical criteria; detection of autoimmune antibodies alone is not exclusionary) 1. Systemic lupus erythematosus 2. Rheumatoid arthritis 3. Adult-onset Still disease 4. Juvenile idiopathic arthritis 5. Autoimmune lymphoproliferative syndrome Malignant/lymphoproliferative disorders (these disorders must be diagnosed before or at the same time as iMCD to be exclusionary): 1. Lymphoma (Hodgkin and non-Hodgkin) 2. Multiple myeloma 3. Primary lymph node plasmacytoma 4. FDC sarcoma 5. POEMS syndrome‡

[a] Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646-1657.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

Consensus Diagnostic Criteria for Idiopathic MCD (continued)[a]

- Select additional features supportive of, but not required for diagnosis
  - Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
  - Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
  - Diagnosis of disorders that have been associated with iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS‡), glomerular nephropathy, inflammatory myofibroblastic tumor

[a] Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646-1657.

Footnotes for CD-B 1 of 2

* Laboratory cutoff thresholds are provided as guidance. Since some laboratories have slightly different ranges, the upper and lower ranges from a particular laboratory should be used to determine if a patient meets a particular laboratory Minor Criterion.

† Evaluation of CRP is mandatory and tracking CRP levels is highly recommended, but ESR will be accepted if CRP is not available.

‡ POEMS is considered to be a disease “associated” with CD. Because the monoclonal plasma cells are believed to drive the cytokine storm, we do not consider it iMCD, but rather “POEMS-associated MCD.”

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED TREATMENT REGIMENS[a]

FIRST-LINE THERAPY (in alphabetical order)		
UCD (surgically unresectable)	**MCD - Criteria for active disease present but no organ failure**	**MCD - Fulminant/severe ± organ failure**
• Rituximab • Rituximab + cyclophosphamide • Rituximab + prednisone • Rituximab + prednisone + cyclophosphamide	***HHV8-negative/HIV-1-negative (iMCD -Nonsevere)*** • Rituximab • Rituximab + prednisone • RCVP (rituximab, cyclophosphamide, vincristine, prednisone) • Siltuximab[b] • Thalidomide + cyclophosphamide + prednisone	***Fulminant/severe HHV8-negative (iMCD)*** • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab • CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) ± rituximab • CVP (cyclophosphamide, vincristine, prednisone) ± rituximab • Siltuximab[b] • If not a candidate for combination therapy: ▸ Rituximab
	HHV8-positive (HIV-1-positive or HIV-1-negative) • Rituximab (preferred) • Rituximab + liposomal doxorubicin • Rituximab + prednisone • Rituximab + prednisone + liposomal doxorubicin • Zidovudine + ganciclovir/valganciclovir	***Fulminant/severe HHV8-positive MCD*** • Rituximab + liposomal doxorubicin • Rituximab + prednisone + liposomal doxorubicin • RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) • RCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) • RCVP (rituximab, cyclophosphamide, vincristine, prednisone) • If not a candidate for combination therapy: ▸ Liposomal doxorubicin ▸ Rituximab

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[b] Tocilizumab is an appropriate option, if there is a shortage of siltuximab or if it is not available.

References on CD-C 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED TREATMENT REGIMENS[a]

SECOND-LINE AND SUBSEQUENT THERAPY FOR RELAPSED/REFRACTORY OR PROGRESSIVE DISEASE (in alphabetical order)

UCD (surgically unresectable)	MCD[c]	
	HHV8(+) - Criteria for active disease present with no organ failure[d] or Fulminant/Severe disease [HHV8(+) or HHV8(-)] with no organ failure	Fulminant/Severe disease [HHV8(+) or HHV8(-)] with organ failure[e]
• Rituximab • Rituximab + cyclophosphamide • Rituximab + prednisone • Rituximab + prednisone + cyclophosphamide • Siltuximab or tocilizumab (if HIV-1-negative/HHV8-negative)	**Preferred regimens** (Add ganciclovir or valganciclovir, if HHV8-positive) • Etoposide (oral or IV) • Liposomal doxorubicin (if HHV8-positive) • Siltuximab[b] (if HHV8-negative) • Vinblastine **Other recommended regimens** • Sirolimus • If not previously given ▸ CHOP ± rituximab ▸ CVAD ± rituximab ▸ CVP ± rituximab	**Preferred regimens** • If not previously given ▸ CHOP ± rituximab ▸ CVAD ± rituximab ▸ CVP ± rituximab ▸ Liposomal doxorubicin ± rituximab (if HHV8-positive) ▸ Siltuximab[b] (if HHV8-negative)
	Subsequent therapy for relapsed/refractory or progressive disease: Alternative regimens • Anakinra • Bortezomib ± rituximab • Lenalidomide ± rituximab • Thalidomide ± rituximab • Tocilizumab • High-dose zidovudine + valganciclovir (if HHV8-positive)	

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[b] Tocilizumab is an appropriate option, if there is a shortage of siltuximab or if it is not available.
[c] Maintenance therapy (optional) for patients with HHV8-positive disease responding to second-line and subsequent therapy.
[d] Treat with alternative first-line therapy regimens (CD-C 1 of 3) before moving onto second-line and subsequent therapy for refractory disease.
[e] Treat with alternate second-line combination therapy regimens ± rituximab (not previously given) before moving onto subsequent therapy with alternative regimens for relpased/refractory or progressive disease.

References on CD-C 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED TREATMENT REGIMENS
REFERENCES

Unicentric Castleman Disease

Bandera B, Ainsworth C, Shikle J, et al. Treatment of unicentric Castleman disease with neoadjuvant rituximab. Chest 2010;138:1239-1241.

van Rhee F, Oksenhendler E, Srkalovic G, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. Blood Adv 2020;4:6039-6050.

Multicentric Castleman Disease

Gerard L, Berezne A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 Castleman B Trial. J Clin Oncol 2007;25:3350-3356.

Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. Blood 2011;117:6977-6986.

Ramasamy K, Gandhi S, Tenant-Flowers M, et al. Rituximab and thalidomide combination therapy for Castleman disease. Br J Haematol 2012;158:421-423.

Uldrick TS, Polizzotto MN, Aleman K, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Blood 2014;124:3544-3552.

van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomized, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-974.

van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132:2115-2124.

Zhang L, Zhao AL, Duan MH, et al. Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease. Blood 2019;133:1720-1728

van Rhee F, Casper C, Voorhees PM, et al. Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Haematol 2020;7:e209-e217.

Rehman MEU, Chattaraj A, Neupane K, et al. Efficacy and safety of regimens used for the treatment of multicentric Castleman disease: A systematic review. Eur J Haematol 2022;109:309-320.

van Rhee F, Rosenthal A, Kanhai K, et al. Siltuximab is associated with improved progression-free survival in idiopathic multicentric Castleman disease. Blood Adv 2022;6:4773-4781.

Pierson SK, Lim MS, Srkalovic G, et al. Treatment consistent with idiopathic multicentric Castleman disease guidelines is associated with improved outcomes. Blood Adv 2023;7:6652-6664.

Liu YT, Gao YH, Zhao H, et al. Sirolimus is effective for refractory/relapsed idiopathic multicentric Castleman disease: A single-center, retrospective study. Ann Hematol 2024;103:4223-4230.

Note: All recommendations are category 2A unless otherwise indicated.

Classification

Table 1

The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)
Mature B-cell lymphomas
HHV-8–associated lymphoproliferative disorders
Multicentric Castleman disease
Primary effusion lymphoma
HHV8-positive diffuse large B-cell lymphoma, NOS
HHV8-positive germinotropic lymphoproliferative disorder

Table 2

WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (2022; 5th edition)
Tumour-like lesions with B-cell predominance
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma
IgG4-related disease
Unicentric Castleman disease
Idiopathic multicentric Castleman disease
KSHV/HHV8-associated multicentric Castleman disease

Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.

WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.

ABBREVIATIONS

C/A/P	chest/abdomen/pelvis
cART	combination antiretroviral therapy
CBC	complete blood count
CD	Castleman disease
CMV	cytomegalovirus
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B-cell lymphoma
EBER-ISH	Epstein-Barr virus-encoded RNA in situ hybridization
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
FDC	follicular dendritic cell
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
GC	germinal center
GI	gastrointestinal
HHV8	human herpesvirus 8
HIV	human immunodeficiency virus
Ig	immunoglobulin
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
iMCD	idiopathic multicentric Castleman disease
IMRT	intensity-modulated radiation therapy
ISRT	involved-site radiation therapy
IVF	in vitro fertilization
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpesvirus
LANA	latency-associated nuclear antigen
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MCD	multicentric Castleman disease
MUGA	multigated acquisition
NGS	next-generation sequencing
NOS	not otherwise specified
PCR	polymerase chain reaction
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes
SPEP	serum protein electrophoresis
TAFRO	thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly
UCD	unicentric Castleman disease
VEGF	vascular endothelial growth factor

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 1.2025
Castleman Disease

Discussion

This discussion corresponds to the NCCN Guidelines for Castleman Disease. Last updated: January 18, 2024.

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NCCN Guidelines Version 1.2025
Castleman Disease

Overview

Castleman disease (CD) is a relatively uncommon heterogenous group of lymphoproliferative disorders with an annual incidence of approximately 4,300–5,200 in the United States.[1] These disorders share common histopathologic features and certain subtypes are associated with an increased risk of developing diffuse large B-cell lymphoma (DLBCL), Kaposi sarcoma (KS), and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome.[2-4]

Unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) are the two main clinical subtypes. In the 2022 newly revised WHO classification of hematolymphoid tumors (WHOHAEM5), UCD and MCD are classified as tumour-like lesions with B-cell predominance.[5] In the 2022 International Consensus Classification, UCD is not included and MCD is classified as HHV-8–associated lymphoproliferative disorders.[6]

MCD is further divided into human herpesvirus 8 (HHV8)-positive (also known as KS herpesvirus [KSHV]-positive), HHV8-negative (also known as idiopathic MCD [iMCD]), and POEMS-MCD.[5] KSHV/HHV8-positive MCD is most commonly diagnosed in people with HIV or otherwise immunocompromised individuals.[7]

iMCD is subclassified into two clinicopathologic subgroups: iMCD-TAFRO (defined by thrombocytopenia [T], anasarca [A], fever [F], reticulin fibrosis of the bone marrow [R], and organomegaly [O] but generally has normal γ-globulin levels) and iMCD-not otherwise specified (NOS), which is typically characterized by hypergammaglobulinemia and thrombocytosis.[8,9]

The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) provide recommendations for diagnostic workup and treatment for UCD and MCD.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Literature Search Criteria

Prior to the initial development of the NCCN Guidelines for Castleman disease, an electronic search of the PubMed database was performed to obtain key literature in Castleman disease. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[10]

The search results were narrowed by selecting relevant studies in humans published in English. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Clinical Presentation

The clinical presentation of CD is often relatively nonspecific with enlarged lymph nodes, lymphadenopathy, and systemic symptoms.

UCD is characterized by involvement of a single lymph node or lymph node station and usually the absence of systemic symptoms. This subtype generally has an indolent disease course with an excellent prognosis. UCD is most commonly (but not always) the histopathologic hypervascular (hyaline vascular) variant and is nearly always HIV negative and HHV8 negative.[7] While often asymptomatic, some patients may experience compression symptoms due to compression of vital organs or other structures.[11-14] In a series of 404 patients with UCD, the most common sites of involvement were the mediastinum (29%), neck (23%), abdomen (21%), and retroperitoneum (17%).[11] In another analysis of 74 patients (43 patients with UCD and 31 patients with iMCD), systemic inflammatory symptoms, elevated inflammatory factors, and abnormal bone marrow features were more common in patients with iMCD than UCD.[12]

MCD is a remitting-relapsing disease with a variable natural history ranging from indolent disease with a very slow progression to acute and fulminant disease.[3,15] HHV8-positive MCD follows a more aggressive course. Immunocompromising conditions is a primary risk factor for HHV8-positive MCD, with HIV being the most common.[16] HHV8-positive MCD is more commonly associated with systemic symptoms such as fluid accumulation, cytopenias, liver and kidney dysfunction, and constitutional symptoms driven by cytokines such as interleukin 6 (IL-6).[12,15,17]

iMCD affects multiple lymph node stations and exhibits lymphadenopathy in more than 1 lymph node or lymph node region. Clinical presentation can range from mild constitutional symptoms to life-threatening organ failure. iMCD-TAFRO generally has a more aggressive disease course and poorer outcomes than iMCD-NOS.[8,9]

Diagnosis

Due to the nonspecific and heterogenous nature of the disease, CD can often mimic other benign and malignant conditions.[2-4] Therefore, a high index of suspicion and histopathologic analysis is required for diagnosis of CD.

Histopathologically, CD has been divided into hypervascular (also called hyaline vascular), plasmacytic, and mixed histologic subtypes.[18] The hypervascular variant is most commonly associated with UCD, whereas the plasmacytic and mixed variants are more common in HHV8-associated MCD. Idiopathic MCD-NOS may exhibit any of the three histologic patterns, whereas MCD-TAFRO is most commonly either hypervascular or mixed.

A combination of clinical, imaging, and pathologic features should be used to establish the diagnosis of UCD, HHV8-positive MCD, and iMCD.[19,20] In an asymptomatic patient, histopathology consistent with CD along with the involvement of a single lymph node or region of lymph nodes can establish a diagnosis of UCD.[20]

In 2017, international diagnostic consensus criteria for the diagnosis of iMCD was published.[19] These diagnostic criteria include two major criteria (histopathologic lymph node features consistent with the iMCD spectrum and enlarged lymph node in at least 2 lymph node stations) and eleven minor criteria (anemia, thrombocytopenia, hypoalbuminemia, polyclonal

hypergammaglobulinemia, renal dysfunction [elevated glomerular filtration rate (GFR) or proteinuria], elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], constitutional symptoms, enlarged spleen and/or liver, fluid accumulation, eruptive cherry hemangiomatosis or violaceous papules, and lymphocytic interstitial pneumonitis). See *Consensus Diagnostic Criteria for Idiopathic MCD (CD-B)* in the algorithm.

The diagnosis of iMCD requires the presence of both major criteria, at least 2 of 11 minor criteria with at least 1 laboratory abnormality, and exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD.[19]

Adequate immunophenotyping of a surgically excised lymph node is required to confirm the diagnosis and exclude malignancy and other diseases.[19] The recommended immunohistochemistry (IHC) panel essential for diagnosis includes: CD20, CD3, CD5, CD138, HHV8, kappa, and lambda. Additional IHC markers may be useful under certain circumstances: Ki-67 index, Ig heavy chains, CD10, BCL2, BCL6, cyclin D1, CD21, CD23, CD38, IRF4/MUM1, and PAX5. Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen of kappa/lambda, CD19, CD20, CD5, CD23, and CD10 may also be useful in certain circumstances. EBER-ISH immunophenotyping is also an essential diagnostic test. Other diagnostic testing that may be useful under certain circumstances includes molecular analysis to detect immunoglobulin and *TCR* gene rearrangements.

Workup

Initial workup should include a physical examination (with attention given to node-bearing areas, liver, and spleen) and evaluation of performance status. Laboratory assessments should include standard blood work including complete blood count (CBC) with differential, and a comprehensive metabolic panel. Serum lactate dehydrogenase (LDH), CRP, and ESR should be measured. Serum protein electrophoresis should be evaluated if there is concern for POEMS syndrome. Pregnancy testing should be done in patients of childbearing potential if chemotherapy or radiation therapy (RT) is planned. PET/CT scan (preferred) or a chest/abdomen/pelvis CT with contrast of diagnostic quality are recommended as part of an initial diagnostic workup to confirm extent of disease and total nodal involvement.[21,22]

Testing to detect the presence of HIV, HHV8, and Epstein-Barr virus (EBV) polymerase chain reaction (PCR) should also be done as part of routine workup. HHV8-positive MCD is distinguished by positive testing for HHV8 in lymph node tissue as well as PCR positivity for HHV8 in plasma in addition to multiple affected lymph nodes and histopathology consistent with CD.[15] Screening for concurrent KS is recommended in the setting of HHV8 or HIV positivity since HHV8-positive MCD may occur with concomitant KS in up to 72% of patients.[23] Hepatitis B testing is an essential component of workup if rituximab-containing regimens are being considered due to the risk of viral reactivation anti-CD20 monoclonal antibody (mAb)-based regimens.

Bone marrow biopsy and aspirate as well as reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome) may be useful under certain circumstances.[24] An echocardiogram or multigated acquisition (MUGA) scan can be considered if anthracycline or anthracenediones are being considered for treatment. Other components of workup that may be useful in certain circumstances include neck CT with contrast, hepatitis C testing, IgG4, sIL6, sIL10, vascular endothelial growth factor (VEGF), uric acid, and ferritin.

Treatment Recommendations

Unicentric Castleman Disease

Surgical resection is the optimal treatment, wherever possible, as it has been associated with very low rates of recurrence and high relapse-free survival (RFS) in multiple case series and retrospective studies.[2,11,14,20,25-27]

One case series of 53 patients reported a 5-year overall survival (OS) rate of 91%,[2] and another retrospective analysis of 278 patients showed an OS rate of over 90% with up to 10-year follow up.[11] Therefore, all patients with a diagnosis of UCD should be evaluated for resectability of disease.[20]

Observation until recurrence is recommended following complete resection. Patients who are asymptomatic following an incomplete resection may be observed until recurrence. Patients who remain symptomatic following incomplete resection should be managed as described below for unresectable disease.

Asymptomatic patients with unresectable UCD should be observed. Available evidence (mostly from case reports) supports the use of RT or rituximab with or without steroids in patients with symptomatic unresectable UCD.[20,28,29] Patients with unresectable disease could be treated with involved-site RT (ISRT) or systemic therapy (rituximab ± prednisone ± cyclophosphamide), with the intent of eventual surgical resection.[20,28,29] Patients with non-bulky disease may be observed after ISRT.

RT should be reserved for severe symptomatic and unresectable disease due to potential long-term complications following RT.[20] The optimal dose of RT in unresectable UCD is not established. Doses as high as 40 Gy in 1.5-2 Gy fractions have been used.[28] Lower doses may be considered depending upon clinical circumstances and advanced radiation techniques are recommended to limit the RT dose to surrounding normal tissues.[30] Embolization may also be considered in certain situations to render surgical resection more feasible and reduce the risk of severe perioperative bleeding.[20]

Treatment options for relapsed/refractory disease are the same as described above for unresectable disease (ISRT or systemic therapy with rituximab ± prednisone ± cyclophosphamide [with the intent of eventual surgical resection] or embolization, if amenable).[20]

Patients with inflammatory symptoms (eg, night sweats, fevers, weight loss) or laboratory disturbances (increased ESR or CRP) may have excessive cytokine production and may benefit from anti-IL-6 mAbs such as siltuximab and tocilizumab, although evidence in this setting is sparse.[20] Siltuximab/tocilizumab is included as an option for relapsed/refractory disease that is HIV-negative and HHV8-negative. Biopsy is encouraged in patients with relapsed/refractory disease to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Overall UCD has an indolent disease course with an excellent prognosis. Careful consideration should be given to the risks and benefits of any therapy for patients with UCD, and observation can be considered in asymptomatic patients.[20]

Multicentric Castleman Disease

Treatment recommendations for MCD are based on the presence of criteria for active disease, presence of fulminant disease, or organ failure and HHV8 status. Patients may experience symptoms related to an excess of IL-6 production; establishing the severity of symptoms is a vital component of management, as severity can vary widely between patients. Corticosteroid monotherapy has a high treatment failure rate but may be combined with other therapies for symptom control. Due to the rarity of the condition, available evidence for most of the treatment options is based on case reports making comparison between treatment options difficult.[21,31,32]

Combination chemotherapy with rituximab is an appropriate treatment option for patients with fulminant HHV8-positive disease with or without organ failure and may be associated with durable remissions.[21,28,31-33] Combination chemotherapy regimen options include R-CHOP, R-CVAD, and R-CVP. Liposomal doxorubicin with or without rituximab is an option, as well as rituximab monotherapy if not a candidate for combination chemotherapy.[34-36]

In patients with criteria for active MCD (fever, increased serum CRP level >20 mg/L in the absence of any other etiology, and at least three other MCD-related symptoms) with no organ failure, first-line therapy options are based on HHV8 status (iMCD [HIV and HHV8 negative] vs. HHV8-positive MCD) as described below.

Patients with POEMS-associated MCD should have treatment directed at POEMS syndrome with regimens recommended for the treatment of multiple myeloma.

Idiopathic MCD

In a double-blind international trial for patients with iMCD, siltuximab (anti-IL-6 mAb) resulted in durable tumor and symptomatic responses in 18 of 53 patients (34%) compared to 26 patients in the placebo group (P = .0012).[37] Long-term follow-up data (median follow-up of 6 years) also established the safety of siltuximab.[38] Siltuximab was also associated with significantly improved progression-free survival (PFS) compared to placebo (median PFS was not reached for siltuximab compared to 15 months for placebo; P = .0001).[39] Adverse events of grade ≥3 were reported in 60% of patients with hypertension (13%), fatigue (8%), nausea (7%), neutropenia (7%), and vomiting (5%) being the most common adverse events.

Siltuximab is FDA approved for the treatment of patients with iMCD that is HIV and HHV8 negative and is the preferred first-line treatment option for this patient population.[38-40] It is worth noting that responses in the pivotal trial were predominant in patients with the plasmacytic or mixed histologic variants and were not seen in hyaline vascular disease where it may have less clinical activity.[37] In patients with disease responding to siltuximab, treatment should be continued until disease progression, as disease may relapse on discontinuation of therapy.[21] Importantly, the clinical trial compared siltuximab with placebo, rather than an active treatment comparator, so it is unknown whether siltuximab is superior to chemoimmunotherapy. Accordingly, chemoimmunotherapy can be considered as an appropriate treatment option in selected patients, particularly in patients with fulminant disease. Chemoimmunotherapy is a time-limited option, unlike siltuximab that is given intravenously every 3 weeks continuously in the absence of progression or intolerance. Patients who receive chemoimmunotherapy as initial treatment may receive siltuximab if needed subsequently for relapsed/refractory disease.

Rituximab (with or without prednisone) and thalidomide, cyclophosphamide and prednisone (TCP) are included as options for other recommended regimens. In a retrospective study of 27 patients with iMCD, rituximab- and cyclophosphamide-containing regimens resulted in an overall response rate of 56% (33% complete response [CR]).[41] In a single-arm, phase 2 study of 25 patients with newly diagnosed iMCD treated with the TCP regimen, primary endpoint (durable tumor and symptomatic response for at least 24 weeks) was achieved in 48% of patients; 12% of patients had stable disease and the estimated 1-year PFS and OS rates were 60% and 88%, respectively.[42]

Patients with disease responding to rituximab-based regimens should be observed until disease progression requiring retreatment. iMCD-TAFRO generally presents as more severe disease, but the evaluation and determination of treatment should be similar to iMCD-NOS.

HHV8-Positive MCD

Rituximab as a single agent or in combination with liposomal doxorubicin or prednisone is the preferred first-line treatment option.[34-36] Combination antiretroviral therapy (cART) should be given to all patients with HIV-positive disease.

The strongest evidence for rituximab monotherapy comes from two phase II studies.[34,35] In one prospective study of rituximab in HIV-associated MCD, 24 patients with relapsed/refractory, chemotherapy-dependent disease were given 4 weekly doses of rituximab at 375 mg/m^2. Twenty-two of the 24 patients were able to become independent of chemotherapy, and

more than three quarters remained free from symptoms and progression 2 years after treatment.[34] In another phase II study of 21 patients with plasmablastic MCD, 20 patients achieved remission of symptoms, and 14 (67%) achieved a radiologic response. The median follow-up was 12 months. The OS and disease-free survival (DFS) rates at 2 years were 95% and 79%, respectively. The main adverse effect was reactivation of KS.[35] In another retrospective analysis of 113 patients (48 had previously received rituximab and 60 were previously diagnosed with KS), treatment with rituximab was associated with a higher 5-year OS rate compared to treatment with chemotherapy alone (90% vs. 47%).[43]

Occult KS is prevalent in HIV/HHV8 (+) MCD and may flare after treatment with rituximab or prednisone.[43] The use of rituximab in combination with liposomal doxorubicin may reduce the incidence of KS exacerbation and may be particularly useful for patients with HHV8-positive MCD with concurrent KS.[36,44] Rituximab has also been shown to decrease the risk of lymphoma in patients with HIV-associated disease.[43]

Zidovudine with either ganciclovir or valganciclovir is also included as a first-line therapy option for HHV8-positive MCD. Zidovudine with valganciclovir has also been shown to be active in HHV8-positive MCD.[44,45] In a study that included 20 patients with HHV8-MCD alone and 34 patients with HHV8-MCD and KS, the 5-year PFS rate was 26% for treatment with the combination of zidovudine and valganciclovir.[44] The median PFS was 6 months. In a pilot study of 14 patients with HHV8-positive MCD, high-dose zidovudine in combination with valganciclovir resulted in major clinical and biochemical responses being attained in 86% and 50% of patients, respectively.[45]

Refractory or Progressive Disease

Biopsy is encouraged in patients with relapsed/refractory disease to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Single-agent therapy is preferred (oral or intravenous etoposide, vinblastine, and liposomal doxorubicin +/- ganciclovir/valganciclovir) for asymptomatic patients with HHV8 (+) disease and no organ failure.[21,31,32] Combination therapy (CHOP, CVAD, CVP) or liposomal doxorubicin +/- rituximab is preferred (if not used in a previous line of therapy) for patients with fulminant disease and organ failure.[21,31,32]

Observation or maintenance with valganciclovir may be considered for HHV8 (+) disease responding to treatment. Alternative single-agent or combination therapy should be considered for disease progression following sequential combination therapies. Options include bortezomib +/- rituximab, thalidomide +/- rituximab, lenalidomide +/- rituximab, high-dose zidovudine + valganciclovir, tocilizumab (anti-IL6 mAb), and anakinra (IL-1 receptor antagonist), based on case reports and case series.[21,44-55]

Tocilizumab is an effective treatment option for patients with MCD that is refractory to rituximab and chemoimmunotherapy.[52-55] An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

High-dose therapy followed by autologous stem cell rescue (HDT/ASCR) may also result in favorable outcomes, particularly for patients with MCD associated with POEMS.[54,56]

References

1. Simpson D. Epidemiology of Castleman Disease. Hematol Oncol Clin North Am 2018;32:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29157611.

2. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. Am J Hematol 2012;87:997-1002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22791417.

3. Muzes G, Sipos F, Csomor J, Sreter L. Multicentric Castleman's disease: a challenging diagnosis. Pathol Oncol Res 2013;19:345-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23516126.

4. Bonekamp D, Hruban RH, Fishman EK. The great mimickers: Castleman disease. Semin Ultrasound CT MR 2014;35:263-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24929266.

5. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732829.

6. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-1253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35653592.

7. Talat N, Schulte KM. Castleman's disease: systematic analysis of 416 patients from the literature. Oncologist 2011;16:1316-1324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21765191.

8. Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol 2016;91:220-226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26805758.

9. Nishimura Y, Hanayama Y, Fujii N, et al. Comparison of the clinical characteristics of TAFRO syndrome and idiopathic multicentric Castleman disease in general internal medicine: a 6-year retrospective study. Intern Med J 2020;50:184-191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31211492.

10. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed January 10, 2024.

11. Talat N, Belgaumkar AP, Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. Ann Surg 2012;255:677-684. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22367441.

12. Yu L, Tu M, Cortes J, et al. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 2017;129:1658-1668. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28100459.

13. Oksenhendler E, Boutboul D, Fajgenbaum D, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. Br J Haematol 2018;180:206-216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29143319.

14. Boutboul D, Fadlallah J, Chawki S, et al. Treatment and outcome of Unicentric Castleman Disease: a retrospective analysis of 71 cases. Br J Haematol 2019;186:269-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31016730.

15. Bower M, Pria AD, Coyle C, et al. Diagnostic criteria schemes for multicentric Castleman disease in 75 cases. J Acquir Immune Defic Syndr 2014;65:e80-82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24442228.

16. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 2001;51:671-679. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11696169.

17. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman

disease in HIV-infected patients. Blood 2000;96:2069-2073. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10979949.

18. Wu D, Lim MS, Jaffe ES. Pathology of Castleman Disease. Hematol Oncol Clin North Am 2018;32:37-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29157618.

19. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646-1657. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28087540.

20. van Rhee F, Oksenhendler E, Srkalovic G, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. Blood Adv 2020;4:6039-6050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33284946.

21. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132:2115-2124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30181172.

22. Koa B, Borja AJ, Aly M, et al. Emerging role of 18F-FDG PET/CT in Castleman disease: a review. Insights Imaging 2021;12:35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33709329.

23. Mylona EE, Baraboutis IG, Lekakis LJ, et al. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev 2008;10:25-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18385778.

24. Belyaeva E, Rubenstein A, Pierson SK, et al. Bone marrow findings of idiopathic Multicentric Castleman disease: A histopathologic analysis and systematic literature review. Hematol Oncol 2022;40:191-201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35104370.

25. Ye B, Gao SG, Li W, et al. A retrospective study of unicentric and multicentric Castleman's disease: a report of 52 patients. Med Oncol 2010;27:1171-1178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19937164.

26. Zhou N, Huang CW, Huang C, Liao W. The characterization and management of Castleman's disease. J Int Med Res 2012;40:1580-1588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22971511.

27. Wong RSM. Unicentric Castleman Disease. Hematol Oncol Clin North Am 2018;32:65-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29157620.

28. Chronowski GM, Ha CS, Wilder RB, et al. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. Cancer 2001;92:670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11505414.

29. Bandera B, Ainsworth C, Shikle J, et al. Treatment of unicentric Castleman disease with neoadjuvant rituximab. Chest 2010;138:1239-1241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21051400.

30. Matthiesen C, Ramgopol R, Seavey J, et al. Intensity modulated radiation therapy (IMRT) for the treatment of unicentric Castlemans disease: a case report and review of the use of radiotherapy in the literature. Radiol Oncol 2012;46:265-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23077466.

31. Rehman MEU, Chattaraj A, Neupane K, et al. Efficacy and safety of regimens used for the treatment of multicentric Castleman disease: A systematic review. Eur J Haematol 2022;109:309-320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35770616.

32. Pierson SK, Lim MS, Srkalovic G, et al. Treatment consistent with idiopathic multicentric Castleman disease guidelines is associated with improved outcomes. Blood Adv 2023;7:6652-6664. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37656441.

33. Herrada J, Cabanillas F, Rice L, et al. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 1998;128:657-662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9537940.

34. Gerard L, Berezne A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25:3350-3356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17664482.

35. Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med 2007;147:836-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18087054.

36. Uldrick TS, Polizzotto MN, Aleman K, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Blood 2014;124:3544-3552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25331113.

37. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-974. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25042199.

38. van Rhee F, Casper C, Voorhees PM, et al. Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Haematol 2020;7:e209-e217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32027862.

39. van Rhee F, Rosenthal A, Kanhai K, et al. Siltuximab is associated with improved progression-free survival in idiopathic multicentric Castleman disease. Blood Adv 2022;6:4773-4781. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35793409.

40. Fajgenbaum DC, Wu D, Goodman A, et al. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease. Am J Hematol 2020;95:1553-1561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32894785.

41. Dong Y, Zhang L, Nong L, et al. Effectiveness of rituximab-containing treatment regimens in idiopathic multicentric Castleman disease. Ann Hematol 2018;97:1641-1647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29732477.

42. Zhang L, Zhao AL, Duan MH, et al. Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease. Blood 2019;133:1720-1728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30760451.

43. Gerard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood 2012;119:2228-2233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22223822.

44. Ramaswami R, Lurain K, Polizzotto MN, et al. Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases. Blood Adv 2021;5:1660-1670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33720337.

45. Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. Blood 2011;117:6977-6986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21487108.

46. Hess G, Wagner V, Kreft A, et al. Effects of bortezomib on pro-inflammatory cytokine levels and transfusion dependency in a patient with multicentric Castleman disease. Br J Haematol 2006;134:544-545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16856889.

47. Sobas MA, Alonso Vence N, Diaz Arias J, et al. Efficacy of bortezomib in refractory form of multicentric Castleman disease associated to poems syndrome (MCD-POEMS variant). Ann Hematol 2010;89:217-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19636554.

48. El-Osta H, Janku F, Kurzrock R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (Anakinra). Mol Cancer Ther 2010;9:1485-1488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20501803.

49. Ramasamy K, Gandhi S, Tenant-Flowers M, et al. Rituximab and thalidomide combination therapy for Castleman disease. Br J Haematol 2012;158:421-423. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22583139.

50. Zhou X, Wei J, Lou Y, et al. Salvage therapy with lenalidomide containing regimen for relapsed/refractory Castleman disease: a report of three cases. Front Med 2017;11:287-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28367597.

51. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106:2627-2632. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15998837.

52. Kawabata H, Kotani S, Matsumura Y, et al. Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. Intern Med 2013;52:1503-1507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23812199.

53. Muzes G, Sipos F, Csomor J, Sreter L. Successful tocilizumab treatment in a patient with human herpesvirus 8-positive and human immunodeficiency virus-negative multicentric Castleman's disease of plasma cell type nonresponsive to rituximab-CVP therapy. APMIS 2013;121:668-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23163599.

54. Jerkeman M, Linden O. Long-term remission in idiopathic Castleman's disease with tocilizumab followed by consolidation with high-dose melphalan--two case studies. Eur J Haematol 2016;96:541-543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26256458.

55. Barlingay G, Findakly D, Hartmann C, Amar S. The Potential Clinical Benefit of Tocilizumab Therapy for Patients with HHV-8-infected AIDS-related Multicentric Castleman Disease: A Case Report and Literature Review. Cureus 2020;12:e7589. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32399323.

56. Abdallah NH, Habermann T, Buadi FK, et al. Multicentric Castleman disease: A single center experience of treatment with a focus on autologous stem cell transplantation. Am J Hematol 2022;97:401-410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35015310.