blood®

International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease

Frits van Rhee, Peter Voorhees, Angela Dispenzieri, Alexander Fosså, Gordan Srkalovic, Makoto Ide, Nikhil Munshi, Stephen Schey, Matthew Streetly, Sheila K. Pierson, Helen L. Partridge, Sudipto Mukherjee, Dustin Shilling, Katie Stone, Amy Greenway, Jason Ruth, Mary Jo Lechowicz, Shanmuganathan Chandrakasan, Raj Jayanthan, Elaine S. Jaffe, Heather Leitch, Naveen Pemmaraju, Amy Chadburn, Megan S. Lim, Kojo S. Elenitoba-Johnson, Vera Krymskaya, Aaron Goodman, Christian Hoffmann, Pier Luigi Zinzani, Simone Ferrero, Louis Terriou, Yasuharu Sato, David Simpson, Raymond Wong, Jean-Francois Rossi, Sunita Nasta, Kazuyuki Yoshizaki, Razelle Kurzrock, Thomas S. Uldrick, Corey Casper, Eric Oksenhendler and David C. Fajgenbaum

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include digital object identifier (DOIs) and date of initial publication.

International, Evidence-based Consensus Treatment Guidelines for Idiopathic Multicentric Castleman Disease

Frits van Rhee,[1] Peter Voorhees,[2] Angela Dispenzieri,[3] Alexander Fosså,[4] Gordan Srkalovic,[5] Makoto Ide,[6] Nikhil Munshi,[7] Stephen Schey,[8] Matthew Streetly,[8] Sheila K. Pierson,[9] Helen L. Partridge,[9] Sudipto Mukherjee,[10] Dustin Shilling,[9] Katie Stone,[1] Amy Greenway,[1] Jason Ruth,[11] Mary Jo Lechowicz,[12] Shanmuganathan Chandrakasan,[13] Raj Jayanthan,[14] Elaine S. Jaffe,[15] Heather Leitch,[16] Naveen Pemmaraju,[17] Amy Chadburn,[18] Megan S. Lim,[19] Kojo S. Elenitoba-Johnson,[19] Vera Krymskaya,[20] Aaron Goodman,[21] Christian Hoffmann,[22] Pier Luigi Zinzani,[23] Simone Ferrero,[24] Louis Terriou,[25] Yasuharu Sato,[26] David Simpson,[27] Raymond Wong,[28] Jean-Francois Rossi,[29] Sunita Nasta,[30] Kazuyuki Yoshizaki,[31] Razelle Kurzrock,[32] Thomas S. Uldrick,[33] Corey Casper,[34] Eric Oksenhendler,[35] and David C. Fajgenbaum[9]

[1]Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC; [3]Division of Hematology/Oncology, Mayo Clinic, Rochester, MN; [4]Department of Oncology, Oslo University Hospital–Norwegian Radium Hospital, Oslo, Norway; [5]Herbert-Herman Cancer Center, Michigan State University College of Human Medicine, Lansing, MI; [6]Department of Hematology, Takamatsu Red Cross Hospital, Takamatsu, Kagawa, Japan; [7]Dana Farber Cancer Institute, VA Boston Healthcare System, Harvard Medical School, Boston, MA; [8]Guys and St. Thomas' NHS Foundation Trust, London, United Kingdom; [9]Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [10]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [11]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [12]Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; [13]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA;

1

[14]Department of Medicine, Baylor College of Medicine, Houston, TX; [15]National Cancer Institute, National Institutes of Health, Bethesda, MD; [16]Division of Hematology, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada; [17] Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [18]Department of Pathology, Weill Cornell Medical College, New York, NY; [19]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [20] Penn Center for Pulmonary Biology, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [21]Department of Medicine, Division of Hematology/Oncology, University of California San Diego, La Jolla, CA, USA; [22]University of Schleswig Holstein, Campus Kiel, Kiel, and ICH Study Center, Hamburg, Germany; [23]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy; [24]Division of Hematology, Department of Molecular Biotechnologies and Health Sciences University of Torino/AOU "Città della Salute e della Scienza di Torino", Turin, Italy; [25]Department of Internal Medicine - Hematology, Hôpital Claude Huriez - CHRU Lille, Lille, France; [26] Division of Pathophysiology, Okayama University Graduate School of Health Sciences, Okayama, Japan; [27]North Shore Hospital, Auckland, New Zealand; [28]Sir Y.K. Pao Centre for Cancer and Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong; [29]Department of Hematology, CHU de Montpellier, Montpellier, France. INSERM U1040, Montpellier, France. Université Montpellier I, Montpellier, France; [30]Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [31]Department of Organic Fine Chemicals, The Institute of Scientific and Industrial Research, Osaka University, Osaka, Japan; [32]Center for Personalized Therapy and Clinical Trials Office, UC San Diego Moore's Cancer Center, La Jolla, CA; [33]Fred Hutch Global Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA; [34]Infectious Disease Research Institute and the Departments of Medicine and Global Health, University of Washington, Seattle, WA; [35]Department of Clinical Immunology, Hôpital Saint-Louis, Paris, France

2

Research Support: None

Corresponding author:

Frits van Rhee MD PhD MRCP(UK) FRCPath FACP

Professor of Medicine & Clinical Director,

Charles and Clydene Scharlau Chair for Hematologic Malignancies Research,

Myeloma Center

University of Arkansas for Medical Sciences,

Mail slot 816

Little Rock, AR 72205

E-mail: vanrheefrits@uams.edu

Fax: (501) 526-2273

Phone: (501) 804-7020 (cell); (501) 526-2873 (office)

Running Head: Therapy for Idiopathic Castleman Disease

Word Count Abstract: 247

Word Count Text: 3966

Table Count: 3

Figure Count: 3

Reference Count: 87

Disclaimers: The Castleman Disease Collaborative Network (CDCN) coordinated the meetings during which the treatment guidelines were developed. The authors of the guidelines had full responsibility for

3

the consensus-building process/methods, data interpretations, treatment recommendations, and writing of

the report.

Abstract

Castleman Disease (CD) describes a group of heterogeneous hematologic disorders with characteristic histopathological features. CD can present with unicentric or multicentric (MCD) regions of lymph node enlargement. Some cases of MCD are caused by human herpesvirus-8 (HHV-8) whereas others are HHV-8-negative/idiopathic (iMCD). Treatment of iMCD is challenging and outcomes can be poor since no uniform treatment guidelines exist, few systematic studies have been conducted, and no agreed upon response criteria have been described. The purpose of this paper is to establish consensus, evidence-based treatment guidelines based on the severity of iMCD to improve outcomes. An international Working Group of 42 experts from ten countries was convened by the Castleman Disease Collaborative Network to establish consensus guidelines for the management of iMCD based on published literature, review of treatment effectiveness for 344 cases and expert opinion. The anti-interleukin-6 monoclonal antibody siltuximab (or tocilizumab, if siltuximab is not available) with or without corticosteroids is the preferred first-line therapy for iMCD. In the most severe cases, adjuvant combination chemotherapy is recommended. Additional agents are recommended, tailored by disease severity, as second- and third-line therapies for treatment failures. Response criteria were formulated to facilitate the evaluation of treatment failure or success. These guidelines should help treating physicians to stratify patients based on disease severity in order to select the best available therapeutic option. An international registry for patients with CD (ACCELERATE, NCT02817997) was established in October 2016 to collect patient outcomes to increase the evidence base for selection of therapies in the future.

Introduction

Dr. Benjamin Castleman described the first case of Castleman Disease (CD) involving a single lymph node station, which is now referred to as unicentric CD (UCD).[1] Characteristic histopathological features observed in CD lymph nodes include hyaline vascular (HV), plasmacytic (PC), and mixed variants.[2,3] CD was later observed to affect multiple lymph node stations, which is known as multicentric CD (MCD).[4] In 1995, Human herpesvirus 8 (HHV-8) was found to be the etiologic agent of a plasmablastic variant of MCD occurring most commonly in HIV-infected or otherwise immunocompromised individuals.[5-10] In HHV-8-associated MCD, viral interleukin-6 (IL-6), a homologue of human IL-6, promotes a pro-inflammatory state accounting for clinical symptomatology and laboratory abnormalities such as anemia, hypoalbuminemia, and elevated C-reactive protein (CRP). In HHV-8-negative MCD, which comprises 33-58% of MCD cases, human IL-6 is the most common pathological driver, but the exact etiology is unknown; this entity is also referred to as "idiopathic MCD" (iMCD).[11-15] We have proposed four etiological hypotheses, including autoimmune, auto-inflammatory, neoplastic, and pathogenic mechanisms, which are now being actively investigated through the Castleman Disease Collaborative Network (CDCN).[12,16]

The presentation of iMCD is quite varied with some patients having mild constitutional symptoms, whilst others develop a life-threatening cytokine storm, organ failure, and death. The diverse clinical presentation calls for a treatment stratagem that takes into account the severity of the disease. Further complicating treatment recommendations is the existence of distinct iMCD sub-types. Some patients experience thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis of the bone marrow (R), and organomegaly (O), but generally have normal gamma-globulin levels, which has recently been referred to as the TAFRO subtype of iMCD.[17,18] Other patients have more classic iMCD with features attributed to IL-6 excess such as thrombocytosis and hyper-gammaglobulinemia, but less extreme anasarca.[18,19] The TAFRO subtype often has more severe clinical symptomatology and worse outcome.[18,20-22] We and others have reported that TAFRO patients have highly vascular lymph nodes and exhibit a different cytokine

6

spectrum with elevated vascular endothelial growth factor (VEGF) levels, but milder elevation of IL-6.[23-25]

Four recent studies in HIV-negative HHV-8 status unknown (believed to be HHV-8-negative) MCD reported 5-year overall survival (OS) rates of 55-77%, reminiscent of the outcomes of malignant disorders, though a large series from tertiary specialty centers reported one-year survival exceeding 90%.[11,26-30] The poor outcome of iMCD may be due to several factors. First, there were no diagnostic criteria for iMCD prior to 2017, when the CDCN published the first-ever consensus diagnostic criteria for iMCD.[23] Second, iMCD is a complex orphan disease with an incidence of 1,000-1,500 cases in the USA.[31] Consequently, few physicians have substantive experience managing iMCD and clinical trials are difficult to conduct. Third, there is a paucity of systematic studies to guide the treating physician, further compounded by the lack of uniform response criteria, hampering evaluation of treatment efficacy. Finally, there are no existing recommendations on how to utilize available treatment modalities in the context of disease severity.

iMCD has been treated with a wide variety of agents including corticosteroids, rituximab, and chemotherapies. More recently, monoclonal antibodies (mAbs) targeting IL-6 directly (siltuximab) or the IL-6 receptor (tocilizumab) have been approved for iMCD therapy.[32,33] However, a significant proportion of patients do not benefit from anti-IL-6 mAbs and additional therapeutic options are needed for non-responders, especially severely-afflicted patients. Herein, we establish comprehensive guidance on the treatment of iMCD based on review of data from 344 patients, published literature, and expert opinion provided by a panel of physicians from the CDCN. The management of HHV-8-associated MCD and POEMS syndrome-associated MCD is well-established and has been reported elsewhere. [34-41]

Methods

An international group of 42 participants from the USA, Japan, China, France, United Kingdom, Germany, Italy, Canada, Norway, and New Zealand, comprised of experts in Hematology/Oncology,

Hematopathology, Infectious Diseases, and Immunology, as well as two physician-patients with iMCD, embarked on the establishment of treatment guidelines for iMCD. The Working Group first met in December 2016 with a follow-up meeting in December 2017. Three additional web-based teleconferences were held in August 2017, November 2017, and March 2018. All relevant English language publications from 1954 to 2017 were identified through PUBMED and other databases using as MESH headings Castleman Disease, Multicentric, and TAFRO. All age groups, including pediatric cases, were included. Clinical trials conducted with siltuximab (NCT00412321, NCT01024036 and NCT01400503) and tocilizumab were also reviewed. Five large datasets as well as individual case reports (see **Supplementary Appendix 1**) served as the primary evidence base.[11,21,32,33,39]

Based on the panel's expert opinion, the impact of different therapeutic interventions was assessed in the context of disease severity, and recommendations for classification of severity and response criteria for evaluation of treatment were derived from the literature. The consensus focused on three main topics: (1) development of iMCD severity criteria, (2) treatment of iMCD, and (3) development of iMCD response criteria. Categories of evidence and consensus were modeled after those developed by the National Comprehensive Cancer Network (https://www.nccn.org/professionals/physician_gls/categories_of_consensus.aspx). A modified Delphi process comprising the integration of evidence provided by the literature and expert opinions was used to generate the final consensus statement contained in this paper, which was approved by all authors.

Data Sharing Statement: All data reviewed for the purposes of generating the consensus criteria was sourced from publicly-available journal articles. A table describing the aggregate data as well as outcome calculations is available as a supplemental appendix.

Results

Management of iMCD

8

To serve as the evidence base for the development of iMCD management guidelines, a dataset of iMCD clinical cases (n = 344) and treatment regimens (n = 479) was assembled (summarized in **Table 1**, complete dataset in **Supplementary Appendix 1**).

Evaluation of iMCD Severity. If a patient is suspected to have iMCD, a comprehensive set of testing is recommended to determine if the patient meets the consensus iMCD diagnostic criteria and assess disease severity (**Table 2**).[23] Laboratory testing for inflammatory markers and organ dysfunction are indicated. Computed tomography (CT) should be performed to visualize the extent of the disease; CT-positron emission tomography (PET) scanning is a useful alternative and high standardized uptake values (>6) should raise the suspicion of an alternative diagnosis *e.g.* lymphoma. The severity of iMCD spans a wide spectrum with some patients exhibiting mild symptomatology, while others experience life-threatening organ failure. Based on expert opinion and review of the evidence base, we recommend assessing the severity of iMCD according to simple criteria (**Figure 1**) to inform the appropriate treatment choice as defined in **Figure 2**. These criteria are intended to segment patients according to their performance status and extent of organ dysfunction into two broad categories: non-severe and severe. Patients with severe iMCD have evidence of organ dysfunction such as renal failure, anasarca, severe anemia, and pulmonary dysfunction resulting in poor performance status likely requiring critical care. Laboratory features include very high CRP levels ($\geq$100g/dL), marked hypoalbuminemia ($\leq$2.0g/dL), and thrombocytopenia ($\leq$100 x 10^{12}/L). Patients with lymphocytic interstitial pneumonitis can also progress to end-stage pulmonary fibrosis if inadequately treated.

Non-severe iMCD. iMCD patients who are not severely sick are typically diagnosed in the outpatient setting and have a good performance status without evidence of abnormal organ function, whilst other patients are more symptomatic and often exhibit an IL-6-driven inflammatory response that interferes significantly with their ability to function and work. Clinical symptoms may be intense enough to require hospitalization, albeit not in intensive care.

9

We recommend (category 1) using anti-IL-6 mAb therapy with siltuximab (11mg/kg every three weeks) for all patients with non-severe iMCD based on the high proportion of responders, the rigorous nature of the studies underlying the evidence base, and the low side effect profile relative to other interventions. Siltuximab, which has been evaluated in a Phase I trial (n = 34), a long-term safety study (n = 19), and a randomized, double-blind placebo-controlled Phase II trial (n =79), is presently approved in the USA, Canada, EU, and Brazil, among other countries.[33,42-47] In the Phase II study, the only randomized controlled trial performed in iMCD to date, 79 patients were allocated to siltuximab 11mg/kg every three weeks or placebo. Durable tumor and symptomatic responses were achieved in 18 of 53 patients in the siltuximab arm [34%; one complete response (CR), 17 partial responses (PRs)] versus zero of 26 in the placebo arm. Nearly 60% of patients had a durable symptomatic response and 31 patients continued to receive unblinded siltuximab.[33] While elevated pre-treatment IL-6 levels are associated with a trend towards an increased likelihood of response to siltuximab, IL-6 levels should not be used to guide treatment decisions. In the Phase II trial, there were iMCD patients with low/normal IL-6 levels who responded to siltuximab while others with high IL-6 levels did not.[45]

If siltuximab is not available, tocilizumab (8mg/kg every two weeks) may be used (category 2A). Tocilizumab, which has undergone an open-label, non-randomized prospective study of 35 patients and been reported extensively in the literature, is approved for the treatment of iMCD in Japan. Like siltuximab, responding patients showed improvement in constitutional symptoms, normalization of abnormal laboratory markers such as CRP, hemoglobin, albumin, and IgG, and reduction in lymphadenopathy with few significant adverse events.[32,48,49] The most common side effects of both siltuximab and tocilizumab are mild thrombocytopenia, hypertriglyceridemia, hypercholesteremia, and pruritus. The availability of siltuximab and tocilizumab varies amongst countries, and the choice between the two drugs is currently more dependent on indication within that country and access, as no head-to-head trials have been performed to compare efficacy.

If needed, first-line therapy with anti-IL6 mAb should be accompanied by corticosteroid therapy for initial disease control. The existing data on corticosteroid monotherapy do not support its use due to limited long-term control and frequent relapses, except in countries where there is no access to mAb therapy.[11,29,50-55] Combining data from published series, we noted a high treatment failure rate at 54% (**Table 1**). Nevertheless, corticosteroids can augment iMCD symptom control along with anti-IL-6 mAbs.[32,33] Patients with more indolent disease can be treated with lower doses of adjunctive corticosteroids (*e.g*. prednisone 1mg/kg, or equivalent for 4-8 weeks followed by tapering; category 2B), whilst patients who are more symptomatic may require higher initial doses of corticosteroids (*e.g*. methylprednisolone 2mg/kg or equivalent) and more gradual tapering.

Careful inspection of the siltuximab and tocilizumab data and the clinical experience of the expert panel suggests that patients with a clear inflammatory syndrome as manifested by symptomatology and biochemical abnormalities are most likely to derive benefit from anti-IL-6 mAb therapy. In the tocilizumab studies virtually all patients had increases in CRP, ESR, and fibrinogen as well significant anemia and hypoalbuminemia.[32,48,49] Though no formal response criteria were employed, 86% of patients remained on therapy for at least five years.[49] In contrast, the symptomatic response rates in patients treated with siltuximab were about 60%, and the combined stringently-defined endpoint of durable symptomatic and lymph node response was 34%. However, the patients in the siltuximab arm of the randomized trial were less severely-affected as reflected by low scores on the MCD symptom scale as well as modest elevations in CRP and fibrinogen, and a median serum albumin that was in the normal range.[33,45,47] Strict exclusion criteria for organ dysfunction and patient selection bias in the randomized siltuximab trial due to a placebo arm likely contributed to the milder phenotype in these patients. Of note, *ad hoc* analysis of the Phase II data revealed that patients demonstrating more clinical and laboratory abnormalities included in the minor criteria of the iMCD diagnostic criteria had a greater response rate than those who did not.[23]

11

Responses in clinical symptomatology occur rapidly with anti-IL-6 mAb therapy and should be apparent after 3-4 doses.[32,46] Laboratory indicators including hemoglobin, CRP, ESR, and albumin should mirror clinical improvements and be followed initially weekly and then bi-weekly until normalization.[33,42,45] Of note, both siltuximab and tocilizumab give rise to spuriously elevated IL-6 levels for 18-24 months following the last dose. Therefore, serum IL-6 levels should not be used to assess response.[14] Resolution of lymphadenopathy can be slow with anti-IL-6 mAb therapy with a median time to lymph node response of five months.[33,46] This is because anti-IL-6 mAbs merely abrogate an important growth signal for lymphocytes and plasma cells, but do not have direct cytotoxic effects. Early response to therapy should be judged using the criteria provided in **Figure 3**, defining symptomatic and biochemical response rather than relying on reduction in lymph node size. Patients should be followed by serial CT-scanning every three months until maximum response has occurred, after which the frequency of imaging can be reduced to six and later 12 months.

Clinical experience of the expert working group with siltuximab and data reported by Nishimoto et al. for tocilizumab suggest that relapses occur on cessation of therapy.[49] Indefinite continuation of anti-IL6 mAb therapy in responding patients is therefore recommended. However, dosing intervals were safely extended to six weeks in 40% of iMCD patients in the long-term safety study of siltuximab, suggesting that dosing may be spaced out in some patients.[44] If used in combination with other agents, steroids should be discontinued as early as possible to minimize side-effects.

We recommend rituximab ($375mg/m^2$ x 4-8 doses) as a first-line alternative to anti-IL6 mAb therapy for patients with non-severe iMCD who do not have marked cytokine-driven symptomatology based on a more limited dataset, since rituximab has not been subjected to systematic study in iMCD and data are confined to case reports or small series (category 2B evidence).[56-61] Most papers report the use of rituximab along with conventional chemotherapies; **Table 1** presents combined data on cytotoxic chemotherapy, which often includes rituximab as a component. In a recently-published study of iMCD patients, the CR and PR rates with rituximab or rituximab-based chemotherapy regimens as first-line

therapy were 20% and 48%, respectively. Rituximab-treated patients had inferior progression-free survival compared to those managed with siltuximab.[21] In two further series, approximately half of the iMCD patients failed rituximab.[11,39] Despite the lack of rigorous evaluation, the available data and expert opinion do support a role for rituximab monotherapy in the treatment of non-severe iMCD patients for whom it would be reasonable to give a limited course of therapy rather than indefinite anti-IL-6 mAb treatment.

It is important to note that approximately 50% of iMCD patients will not achieve a satisfactory response to first-line anti-IL6 therapy. Failure to achieve a satisfactory response, defined as PR or CR (**Figure 3**), to first-line therapy should prompt re-evaluation of the original diagnosis to rule out an alternative diagnosis such as lymphoma. Anti-IL6 mAb treatment does not need to be continued if it was not effective in first-line. Second-line therapy should comprise rituximab to which immunomodulatory/immunosuppressive agents (see below) and steroids may be added. Thalidomide has been combined with rituximab and steroids since it downregulates IL-6 expression and has anti-angiogenic properties by modulating VEGF. Thalidomide has induced remissions in iMCD as a single agent and has also been valuable in combination with rituximab in both HHV-8-associated MCD and iMCD (Schey, personal communication).[62-64]

Third-line therapy for patients who fail both anti-IL-6 mAbs and rituximab is less well-defined. Cytotoxic chemotherapies have a high response rate in our pooled data analysis (78%), but treatment failure with relapses are common (42%) and toxicities are significant (**Table 1**). Therefore, the consensus opinion is to avoid cytotoxic chemotherapy unless the patient progresses to severe iMCD. We recommend use of an immunomodulatory/immunosuppressive agent since these agents have less toxicity than chemotherapy and have similar efficacy (69% response), albeit in fewer case reports.[62-64,66-71,72] These agents include cyclosporine A, sirolimus, thalidomide, lenalidomide, bortezomib, the IL-1β receptor antagonist anakinra, retinoic acid derivatives, and interferon-α.[62,63,65-72,73] Cyclosporine A has been used most extensively in iMCD-TAFRO cases, particularly to improve persistent ascites and

thrombocytopenia.[20,74-77] Anakinra, which blocks the IL-1β receptor and presumably NF-kB signaling, has been reported as successful treatment of a siltuximab-refractory iMCD patient.[67,68]

Severe iMCD: How to Treat the Critically Ill Patient. Based on published data, the proportion of patients with severe iMCD, who have marked organ dysfunction, poor performance status, and require critical care, is estimated to be 10-20%.[11,21] These patients should be promptly started on a high-dose steroid regimen (*e.g.* methylprednisolone 500mg daily) together with siltuximab. For pharmacokinetic reasons, an accelerated, weekly dosing schedule of siltuximab may be used for one month. Patients who immediately respond should continue on siltuximab at every three week intervals indefinitely and slowly taper steroids.

There is consensus in the Working Group that patients with severe iMCD are at significant risk of mortality and expert advice should be sought. Severe iMCD may not respond immediately to high-dose steroids and anti-IL-6 mAbs, which can take weeks to achieve steady state concentration. Still others may never respond to anti-IL-6 mAbs. Therefore, aggressive intervention with multi-agent chemotherapy should be considered as early as necessary (any sign of deterioration or after one week of no response to siltuximab, whichever comes first) to ablate the hyperactivated immune system and stem the cytokine storm. Chemotherapy regimens including those for lymphoma: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), or CVP (cyclophosphamide, vincristine, prednisone); myeloma: VDT-ACE-R (bortezomib, dexamethasone, thalidomide, doxorubicin, cyclophosphamide, etoposide, rituximab); or etoposide/cyclophosphamide-containing regimens as used for hemophagocytic lymphohistiocytosis have all been employed.[18,50,54,78] Combination chemotherapy is appropriate in poor performance status patients, including those requiring treatment in the intensive care unit, as control of the cytokine storm can be life-saving and bring about rapid improvement. As per **Table 1**, cytotoxic chemotherapy has the highest overall response rate (78%), but considerable toxicities and frequent relapses deter its use outside of the most severe setting when the risk/benefit analysis is skewed.[29,52,79]

The subsequent management of severe iMCD patients who fail to respond to anti-IL-6 mAb or the first cytotoxic chemotherapy regimen, or those who relapse, is not well-defined and is mostly done on an *ad hoc* basis taking into account any previous response, clinical status, co-morbidities, and cytokine profile. Patients who have elevation of IL-6 prior to starting anti-IL-6 mAb therapy may still benefit from extended therapy with anti-IL-6 mAb, even if they did not respond during the acute episode, whilst others may respond to immunomodulators/immunosuppressants or salvage cytotoxic therapy more commonly used in plasma cell malignancies *e.g*. VTD (bortezomib, thalidomide, dexamethasone). Autologous and allogeneic stem cell transplantation have only been reported in a few cases with mixed results and are therapies of last resort.[80-83]

Severe iMCD often presents as the TAFRO subtype. Our analysis of 49 published iMCD-TAFRO cases with treatment data revealed that corticosteroids, anti-IL-6 mAbs, cytotoxic chemotherapies, and cyclosporine A are most often used. These agents demonstrate initial similar efficacy to the other cohorts, but higher rates of treatment failures and relapses (**Table 3**). Based on the available evidence, we recommend following the same treatment algorithm as for other cases of iMCD that is dependent on disease severity and initiate therapy with anti-IL-6 mAb therapy with or without corticosteroids. Among TAFRO cases, cyclosporine A can be useful therapy for anti-IL-6-refractory cases particularly to improve persistent ascites and thrombocytopenia.[21,74-77] The Japanese TAFRO research group recommends high-dose steroids, tocilizumab and cyclosporine A for patients with TAFRO syndrome.[84] A comprehensive analysis of a treatment-refractory iMCD-TAFRO patient who sustained multiple relapses after repeated cycles of chemotherapy showed upregulation of the mTOR pathway, and remission was successfully maintained with sirolimus.[85] Early data suggest that the proteomic profiles of classical and TAFRO-iMCD are different, supporting the notion that there may be diverse chemokines/cytokines driving the symptomatology across the iMCD spectrum.[24,25]

Evaluation of Response. As is evident from the review of published literature, criteria for response to treatment of iMCD have thus far not been agreed upon. In the tocilizumab study, the primary endpoint

was based on improvements in specific laboratory tests, but there was no aggregated response definition.[32] The Phase I siltuximab study used Cheson criteria for lymph node response modified to assess the skin lesions of iMCD. This trial introduced a clinical benefit response assessing six iMCD-related clinical features.[42,86] In the Phase II registration study of siltuximab, lymphadenopathy was similarly assessed, but the symptomatic response was evaluated by the investigators using a complex 34 iMCD-related symptom score.[33]

The FDA, in its approval of siltuximab, commented on the necessity of a composite response assessment for iMCD.[87] Therefore, our expert panel established a composite end-point for evaluating response taking into account all cardinal features of the disease: a) objective biochemical markers of inflammatory response and organ function (hemoglobin, CRP, albumin, estimated glomerular filtration rate), b) lymph node size, and c) clinical symptoms (fatigue, anorexia, fever, weight change) as assessed by the clinician (**Figure 3**).

A biochemical CR requires normalization of all values compared to baseline. In a PR, there is 50-99% improvement in all laboratory values. In patients with stable disease (SD), there is a <50% improvement in all laboratory values or <25% worsening in any laboratory indicators. Progressive disease (PD) indicates a >25% worsening in any of the laboratory markers. Lymph node response is assessed using modified Cheson criteria as previously published.[42,86] Lastly, four important clinical symptoms are assessed using the National Cancer Institute Common Terminology Criteria of Adverse Events (version 4). A symptomatic CR requires normalization of all symptoms. PR requires improvement in the grades of all 4 symptoms, but they do not have to return to baseline. SD requires not meeting the criteria for PR or PD, which occurs if any symptoms worsen on $\geq$ 2 assessments four weeks apart. Evaluation of overall response requires integration of the three response categories as defined in **Figure 3.**

Discussion

The published diagnostic criteria of iMCD, together with the recognition of the TAFRO-iMCD subtype, provides a framework for recognizing different clinical entities on the CD spectrum.[18,23] We present the first formal guidelines for the treatment of iMCD, depending on symptom severity. Based on the response criteria used in the literature and our clinical expertise, we propose composite response criteria addressing all relevant features of the disease to evaluate treatment in both clinical practice and future studies. The present guidelines should assist physicians with selecting therapy and evaluating response, thereby improving patient outcomes. The preferred treatment for non-severe iMCD is siltuximab, whilst for some patients with limited symptomatology, a short course of rituximab is an alternative option. Patients with severe iMCD are a challenge and may require early intervention with combination chemotherapy to avoid a fatal outcome. Not all patients will benefit from siltuximab therapy, especially those who have a very mild inflammatory syndrome, or on the other end of the spectrum, severely-ill patients who require a rapid response. Lastly, it has become clear that iMCD has a pleomorphic cytokine profile and that the disease is not driven by IL-6 in all.

There are several important limitations to our treatment recommendations. It is important to highlight that most recommendations were reached by consensus and are not supported by prospective, randomized data. Due to the rarity of the disease, there are no clinical studies available comparing treatment modalities such as chemotherapy, rituximab, and anti-IL6 mAbs. Though the evidence base included clinical trial data and the largest collection of treatment data analyzed to date, it should be noted that case reports and retrospective case series with short follow-up durations make up a large portion of cases, which are subject to publication bias of successful uses of novel agents. Additionally, the various studies used different criteria for assessing response (CR, PR, "response"); *e.g.* the threshold for a CR in a randomized controlled trial is likely different from that in a case report. Therefore, we aggregated all response categories into one global response category, which is listed in **Table 1**. We included a broad range of data from multiple sources to minimize these limitations. Although anti-IL-6 mAbs are an

17

important contribution to the therapeutic armamentarium for iMCD, treatment must be continued long term. The CDCN established an international registry (www.CDCN.org/ACCELERATE), which collects data pertaining to treatment and outcome, to increase the evidence base for selection of therapies in the future. Ongoing research will focus on defining the etiology and pathogenesis of this complex and rare disease to promote the development of better and more targeted therapies, particularly for patients who do not benefit from anti-IL-6 mAb administration.

Authorship and Conflict of Interest Statements

18

REFERENCES

1.   Castleman B, Towne VW. Case Records of the Massachusetts General Hospital; Weekly

        Clinicopathological Exercises; Founded by Richard C. Cabot. *N. Engl. J. Med*. 1954;251(10):396-

        400.

2.   Flendrig J. Benign Giant Lymphoma: The Clincal Signs and Symptoms and the Morphological

        Aspects. *Folia Medica*. 1969;12:119-120.

3.   Keller AR, Hochholzer L, Castleman B. Hyaline-Vascular and Plasma-Cell Types of Giant Lymph

        Node Hyperplasia of the Mediastinum and Other Locations. *Cancer*. 1972;29(3):670-683.

4.   Gaba AR, Stein RS, Sweet DL, Variakojis D. Multicentric Giant Lymph Node Hyperplasia. *Am. J.

        Clin. Pathol*. 1978;69(1):86-90.

5.   Lachant NA, Sun NC, Leong LA, Oseas RS, Prince HE. Multicentric Angiofollicular Lymph

        Node Hyperplasia (Castleman's Disease) Followed by Kaposi's Sarcoma in Two Homosexual

        Males with the Acquired Immunodeficiency Syndrome (AIDS). *Am. J. Clin. Pathol*.

        1985;83(1):27-33.

6.   Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's Sarcoma-Associated Herpesvirus-Like DNA

        Sequences in Multicentric Castleman's Disease. *Blood*. 1995;86(4):1276-1280.

7.   Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's Disease in HIV Infection: A

        Clinical and Pathological Study of 20 Patients. *AIDS (London, England)*. 1996;10(1):61-67.

8.   Aoki Y, Tosato G, Fonville TW, Pittaluga S. Serum Viral Interleukin-6 in AIDS-Related

        Multicentric Castleman Disease. *Blood*. 2001;97(8):2526-2527.

9.   Dossier A, Meignin V, Fieschi C, Boutboul D, Oksenhendler E, Galicier L. Human Herpesvirus 8-

        Related Castleman Disease in the Absence of HIV Infection. *Clinical Infectious Diseases : An

        Official Publication of the Infectious Diseases Society of America*. 2013;56(6):833-842.

10.   Nicoli P, Familiari U, Bosa M, et al. HHV8-Positive, HIV-Negative Multicentric Castleman's Disease: Early and Sustained Complete Remission with Rituximab Therapy without Reactivation of Kaposi Sarcoma. *Int. J. Hematol.* 2009.

11.   Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic Multicentric Castleman's Disease: A Systematic Literature Review. *The Lancet. Haematology.* 2016;3(4):e163-175.

12.   Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-Negative, Idiopathic Multicentric Castleman Disease: Novel Insights into Biology, Pathogenesis, and Therapy. *Blood.* 2014;123(19):2924-2933.

13.   Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic Significance of Interleukin-6 (IL-6/BSF-2) in Castleman's Disease. *Blood.* 1989;74(4):1360-1367.

14.   Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and Pathologic Significances in Increase in Serum Interleukin-6 (IL-6) and Soluble IL-6 Receptor after Administration of an Anti-IL-6 Receptor Antibody, Tocilizumab, in Patients with Rheumatoid Arthritis and Castleman Disease. *Blood.* 2008;112(10):3959-3964.

15.   Stone K, Woods E, Szmania SM, et al. Interleukin-6 Receptor Polymorphism is Prevalent in HIV-Negative Castleman Disease and is Associated with Increased Soluble Interleukin-6 Receptor Levels. *PLoS One.* 2013;8(1):e54610.

16.   Fajgenbaum DC, Ruth JR, Kelleher D, Rubenstein AH. The Collaborative Network Approach: A New Framework to Accelerate Castleman's Disease and Other Rare Disease Research. *The Lancet. Haematology.* 2016;3(4):e150-152.

17.   Iwaki N, Sato Y, Takata K, et al. Atypical Hyaline Vascular-Type Castleman's Disease with Thrombocytopenia, Anasarca, Fever, and Systemic Lymphadenopathy. *Journal of Clinical and Experimental Hematopathology : JCEH.* 2013;53(1):87-93.

18. 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(2):220-226.

19. 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. *Internal Medicine (Tokyo, Japan)*. 2013;52(13):1503-1507.

20. Takai K, Nikkuni K, Shibuya H, Hashidate H. [Thrombocytopenia with Mild Bone Marrow Fibrosis Accompanied by Fever, Pleural Effusion, Ascites and Hepatosplenomegaly]. *[Rinsho ketsueki] The Japanese Journal of Clinical Hematology*. 2010;51(5):320-325.

21. Yu L, Tu M, Cortes J, et al. Clinical and Pathological Characteristics of HIV- and HHV-8-Negative Castleman Disease. *Blood*. 2017;129(12):1658-1668.

22. Igawa T, Sato Y. TAFRO Syndrome. *Hematol. Oncol. Clin. North Am*. 2018;32(1):107-118.

23. 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(12):1646-1657.

24. Iwaki N, Gion Y, Kondo E, et al. Elevated Serum Interferon Gamma-Induced Protein 10 kDa is Associated with TAFRO Syndrome. *Sci. Rep*. 2017;7:42316.

25. Pierson S, Stonestrom A, Ruth J, et al. Quantification of Plasma Proteins from Idiopathic Multicentric Castleman Disease Flares and Remissions Reveals 'Chemokine Storm' and Separates Clinical Subtypes. *ASH Annual Meeting Abstracts*. 2017;130:3592.

26. Talat N, Schulte KM. Castleman's Disease: Systematic Analysis of 416 Patients from the Literature. *The Oncologist*. 2011;16(9):1316-1324.

27. Dispenzieri A, Armitage JO, Loe MJ, et al. The Clinical Spectrum of Castleman's Disease. *Am. J. Hematol*. 2012;87(11):997-1002.

28. Shin DY, Jeon YK, Hong YS, et al. Clinical Dissection of Multicentric Castleman Disease. *Leuk. Lymphoma*. 2011;52(8):1517-1522.

29. Seo S, Yoo C, Yoon DH, et al. Clinical Features and Outcomes in Patients with Human Immunodeficiency Virus-Negative, Multicentric Castleman's Disease: A Single Medical Center Experience. *Blood Res*. 2014;49(4):253-258.

30. Robinson D, Jr., Reynolds M, Casper C, et al. Clinical Epidemiology and Treatment Patterns of Patients with Multicentric Castleman Disease: Results from Two US Treatment Centres. *Br. J. Haematol*. 2014;165(1):39-48.

31. Simpson D. Epidemiology of Castleman Disease. *Hematol. Oncol. Clin. North Am*. 2018;32(1):1-10.

32. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized Anti-Interleukin-6 Receptor Antibody Treatment of Multicentric Castleman Disease. *Blood*. 2005;106(8):2627-2632.

33. 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(9):966-974.

34. Marcelin AG, Aaron L, Mateus C, et al. Rituximab Therapy for HIV-Associated Castleman Disease. *Blood*. 2003;102(8):2786-2788.

35. Hoffmann C, Schmid H, Muller M, et al. Improved Outcome with Rituximab in Patients with HIV-Associated Multicentric Castleman Disease. *Blood*. 2011;118(13):3499-3503.

36. Bower M, Powles T, Williams S, et al. Brief Communication: Rituximab in HIV-Associated Multicentric Castleman Disease. *Ann. Intern. Med*. 2007;147(12):836-839.

37. 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(10):2228-2233.

38. 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(24):3544-3552.

39. 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(2):206-216.

40. Bower M. How I Treat HIV-Associated Multicentric Castleman Disease. *Blood*. 2010;116(22):4415-4421.

41. Dispenzieri A. POEMS Syndrome: 2017 Update on Diagnosis, Risk Stratification, and Management. *Am. J. Hematol*. 2017;92(8):814-829.

42. van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a Novel Anti-Interleukin-6 Monoclonal Antibody, for Castleman's Disease. *J. Clin. Oncol*. 2010;28(23):3701-3708.

43. Kurzrock R, Voorhees PM, Casper C, et al. A Phase I, Open-Label Study of Siltuximab, an Anti-IL-6 Monoclonal Antibody, in Patients with B-Cell Non-Hodgkin Lymphoma, Multiple Myeloma, or Castleman Disease. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*. 2013;19(13):3659-3670.

44. van Rhee F, Casper C, Voorhees PM, et al. A Phase 2, Open-Label, Multicenter Study of the Long-Term Safety of Siltuximab (an Anti-Interleukin-6 Monoclonal Antibody) in Patients with Multicentric Castleman Disease. *Oncotarget*. 2015;6(30):30408-30419.

45. Casper C, Chaturvedi S, Munshi N, et al. Analysis of Inflammatory and Anemia-Related Biomarkers in a Randomized, Double-Blind, Placebo-Controlled Study of Siltuximab (Anti-IL6 Monoclonal Antibody) in Patients with Multicentric Castleman Disease. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*. 2015;21(19):4294-4304.

46. van Rhee F, Munshi N, Wong R, et al. Efficacy of Siltuximab in Patients with Previously Treated Multicentric Castleman's Disease (MCD). *J. Clin. Oncol*. 2014;32(5s):suppl; abstr 8514, Oral Abstract Session.

47. van Rhee F, Rothman M, Ho KF, et al. Patient-Reported Outcomes for Multicentric Castleman's Disease in a Randomized, Placebo-Controlled Study of Siltuximab. *Patient*. 2015;8(2):207-216.

48.   Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's Disease by Humanized Anti-Interleukin-6 Receptor Antibody Therapy. *Blood*. 2000;95(1):56-61.

49.   Nishimoto N, Honda O, Sumikawa H, Johkoh T, Aozasa K, Kanakura Y. A Long-Term (5-Year) Sustained Efficacy of Tocilizumab for Multicentric Castleman's Disease and the Effect on Pulmonary Complications. *Blood*. 2007;110.

50.   Herrada J, Cabanillas F, Rice L, Manning J, Pugh W. The Clinical Behavior of Localized and Multicentric Castleman Disease. *Ann. Intern. Med*. 1998;128(8):657-662.

51.   Bowne WB, Lewis JJ, Filippa DA, et al. The Management of Unicentric and Multicentric Castleman's Disease: A Report of 16 Cases and a Review of the Literature. *Cancer*. 1999;85(3):706-717.

52.   Chronowski GM, Ha CS, Wilder RB, Cabanillas F, Manning J, Cox JD. Treatment of Unicentric and Multicentric Castleman Disease and the Role of Radiotherapy. *Cancer*. 2001;92(3):670-676.

53.   Kessler E. Multicentric Giant Lymph Node Hyperplasia. A Report of Seven Cases. *Cancer*. 1985;56(10):2446-2451.

54.   Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric Angiofollicular Lymph Node Hyperplasia: A Clinicopathologic Study of 16 Cases. *Hum. Pathol*. 1985;16(2):162-172.

55.   Frizzera G, Peterson BA, Bayrd ED, Goldman A. A Systemic Lymphoproliferative Disorder with Morphologic Features of Castleman's Disease: Clinical Findings and Clinicopathologic Correlations in 15 Patients. *J. Clin. Oncol*. 1985;3(9):1202-1216.

56.   Ocio EM, Sanchez-Guijo FM, Diez-Campelo M, et al. Efficacy of Rituximab in an Aggressive Form of Multicentric Castleman Disease Associated with Immune Phenomena. *Am. J. Hematol*. 2005;78(4):302-305.

57.   Ide M, Ogawa E, Kasagi K, Kawachi Y, Ogino T. Successful Treatment of Multicentric Castleman's Disease with Bilateral Orbital Tumour Using Rituximab. *Br. J. Haematol*. 2003;121(5):818-819.

58.   Gholam D, Vantelon JM, Al-Jijakli A, Bourhis JH. A Case of Multicentric Castleman's Disease Associated with Advanced Systemic Amyloidosis Treated with Chemotherapy and Anti-CD20 Monoclonal Antibody. *Ann. Hematol*. 2003;82(12):766-768.

59.   Ide M, Kawachi Y, Izumi Y, Kasagi K, Ogino T. Long-Term Remission in HIV-Negative Patients with Multicentric Castleman's Disease Using Rituximab. *Eur. J. Haematol*. 2006;76(2):119-123.

60.   Mian H, Leber B. Mixed Variant Multicentric Castleman Disease Treated with Rituximab: Case Report. *J. Pediatr. Hematol. Oncol*. 2010;32(8):622.

61.   Adam Z, Szturz P, Koukalova R, et al. [PET-CT Documented Remission of Multicentric Castleman Disease after Treatment with Rituximab: Case Report and Review]. *Vnitrni lekarstvi*. 2015;61(3):251-259.

62.   Lee FC, Merchant SH. Alleviation of Systemic Manifestations of Multicentric Castleman's Disease by Thalidomide. *Am. J. Hematol*. 2003;73(1):48-53.

63.   Starkey CR, Joste NE, Lee FC. Near-Total Resolution of Multicentric Castleman Disease by Prolonged Treatment with Thalidomide. *Am. J. Hematol*. 2006;81(4):303-304.

64.   Ramasamy K, Gandhi S, Tenant-Flowers M, et al. Rituximab and Thalidomide Combination Therapy for Castleman Disease. *Br. J. Haematol*. 2012;158(3):421-423.

65.   Tatekawa S, Umemura K, Fukuyama R, et al. Thalidomide for Tocilizumab-Resistant Ascites with TAFRO Syndrome. *Clin Case Rep*. 2015;3(6):472-478.

66.   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(2):287-292.

67.   Galeotti C, Tran TA, Franchi-Abella S, Fabre M, Pariente D, Kone-Paut I. IL-1Ra Agonist (Anakinra) in the Treatment of Multifocal Castleman Disease: Case Report. *J. Pediatr. Hematol. Oncol.* 2008;30(12):920-924.

68.   El-Osta H, Janku F, Kurzrock R. Successful Treatment of Castleman's Disease with Interleukin-1 Receptor Antagonist (Anakinra). *Mol. Cancer Ther.* 2010;9(6):1485-1488.

69.   Hess G, Wagner V, Kreft A, Heussel CP, Huber C. Effects of Bortezomib on Pro-Inflammatory Cytokine Levels and Transfusion Dependency in a Patient with Multicentric Castleman Disease. *Br. J. Haematol.* 2006;134(5):544-545.

70.   Yuan ZG, Dun XY, Li YH, Hou J. Treatment of Multicentric Castleman's Disease Accompanying Multiple Myeloma with Bortezomib: A Case Report. *J. Hematol. Oncol.* 2009;2:19.

71.   Lin Q, Fang B, Huang H, et al. Efficacy of Bortezomib and Thalidomide in the Recrudescent Form of Multicentric Mixed-Type Castleman's Disease. *Blood Cancer Journal.* 2015;5:e298.

72.   Rieu P, Droz D, Gessain A, Grunfeld JP, Hermine O. Retinoic Acid for Treatment of Multicentric Castleman's Disease. *Lancet.* 1999;354(9186):1262-1263.

73.   Miltenyi Z, Toth J, Gonda A, Tar I, Remenyik E, Illes A. Successful Immunomodulatory Therapy in Castleman Disease with Paraneoplastic Pemphigus Vulgaris. *Pathology Oncology Research : POR.* 2009;15(3):375-381.

74.   Takasawa N, Sekiguchi Y, Takahashi T, Muryoi A, Satoh J, Sasaki T. A Case of TAFRO Syndrome, a Variant of Multicentric Castleman's Disease, Successfully Treated with Corticosteroid and Cyclosporine A. *Mod Rheumatol.* 2016:1-5.

75.   Yamaga Y, Tokuyama K, Kato T, et al. Successful Treatment with Cyclosporin a in Tocilizumab-Resistant TAFRO Syndrome. *Internal Medicine (Tokyo, Japan).* 2016;55(2):185-190.

76.   Konishi Y, Takahashi S, Nishi K, et al. Successful Treatment of TAFRO Syndrome, a Variant of Multicentric Castleman's Disease, with Cyclosporine A: Possible Pathogenetic Contribution of Interleukin-2. *The Tohoku Journal of Experimental Medicine.* 2015;236(4):289-295.

77. Inoue M, Ankou M, Hua J, Iwaki Y, Hagihara M, Ota Y. Complete Resolution of TAFRO Syndrome (Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis and Organomegaly) after Immunosuppressive Therapies Using Corticosteroids and Cyclosporin A : A Case Report. *Journal of Clinical and Experimental Hematopathology : JCEH*. 2013;53(1):95-99.

78. Frizzera G. Castleman's Disease and Related Disorders. *Semin. Diagn. Pathol*. 1988;5(4):346-364.

79. Zhu SH, Yu YH, Zhang Y, Sun JJ, Han DL, Li J. Clinical Features and Outcome of Patients with HIV-Negative Multicentric Castleman's Disease Treated with Combination Chemotherapy: A Report on 10 Patients. *Med Oncol*. 2013;30(1):492.

80. 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(5):541-543.

81. Tal Y, Haber G, Cohen MJ, et al. Autologous Stem Cell Transplantation in a Rare Multicentric Castleman Disease of the Plasma Cell Variant. *Int. J. Hematol*. 2011;93(5):677-680.

82. Ogita M, Hoshino J, Sogawa Y, et al. Multicentric Castleman Disease with Secondary AA Renal Amyloidosis, Nephrotic Syndrome and Chronic Renal Failure, Remission after High-Dose Melphalan and Autologous Stem Cell Transplantation. *Clin. Nephrol*. 2007;68(3):171-176.

83. Angenendt L, Kerkhoff A, Wiebe S, et al. Remissions of Different Quality Following Rituximab, Tocilizumab and Rituximab, and Allogeneic Stem Cell Transplantation in a Patient with Severe Idiopathic Multicentric Castleman's Disease. *Ann. Hematol*. 2015;94(7):1241-1243.

84. Masaki Y, Kawabata H, Takai K, et al. Proposed Diagnostic Criteria, Disease Severity Classification and Treatment Strategy for TAFRO Syndrome, 2015 Version. *Int. J. Hematol*. 2016;103(6):686-692.

85. Fajgenbaum D, Shilling D, Partridge HL, et al. Prolonged Remission Achieved in a Relapsing Idiopathic Multicentric Castleman Disease Patient with a Novel, Targeted Treatment Approach. *ASH Annual Meeting Abstracts*. 2017;130:3593.

86.   Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. NCI Sponsored International Working Group. *J. Clin. Oncol*. 1999;17(4):1244.

87.   Deisseroth A, Ko CW, Nie L, et al. Fda Approval: Siltuximab for the Treatment of Patients with Multicentric Castleman Disease. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*. 2015;21(5):950-954.

Figure Legends.

Figure 1. CDCN Severity Classification for Rapid Assessment and Allocation of Therapy. Patients with severe iMCD must have at least two of the five criteria listed above. Patients should be classified as non-severe iMCD if the above criteria are not met.

Figure 2. Treatment Algorithm for iMCD. iMCD patients should be stratified for disease severity per **Figure 1**. **Non-Severe iMCD**: Siltuximab is recommended as frontline therapy for patients with non-severe iMCD. Tocilizumab can be used if siltuximab is not available or approved. Steroids are useful adjunctive therapy and the dose can be tailored according to the severity of the disease. Patients responding to anti-IL6 mAb therapy should be continued indefinitely. *For patients with mild symptomatology, a limited course of rituximab is an alternative option. Patients not responding to anti-IL6 mAb therapy should be considered for rituximab-based therapy + steroids ± immunomodulatory/immunosuppressive agents. ♣Immunomodulatory/immunosuppressive agents for second or third line therapy include thalidomide, cyclosporine A, sirolimus, anakinra, or bortezomib, but we recommend consulting with an expert at this stage.

 Severe iMCD: Severe disease must be closely monitored, as life-threatening events may occur in this population. Severely ill patients should be treated with siltuximab and high-dose steroids, but if no clear response occurs within one week (or if status worsens at any time), then combination chemotherapy should be considered. When possible, expert advice should be sought to identify the most appropriate therapy for a given patient. Further therapy is best individualized. †Examples of chemotherapy include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-VDT-PACE (rituximab, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide), or etoposide/ cyclophosphamide/rituximab. Siltuximab is the preferred anti-IL-6 therapy. However, in countries where siltuximab is not available or approved, tocilizumab can be used instead. Supporting evidence category 1, green boxes, category 2A, yellow boxes; category 2B, blue boxes.

Figure 3. CDCN Response Criteria Based on Evaluation of Biochemical, Lymph Node, and Symptom Response. Biochemical, lymph node, and response criteria have been detailed in the text. For lymph node response, Cheson criteria have been modified to include assessment of skin manifestations.[42] An overall CR requires a complete biochemical, lymph node and symptomatic response. An overall PR requires nothing less than a PR across all categories, but not meeting criteria for CR. Overall SD requires no PD in any of the categories and not meeting the criteria for CR or PR. An overall PD occurs when any category has a PD. Symptomatic and biochemical response evaluation should be done on a monthly basis until maximum response has been achieved. Radiological assessment of lymph node response by CT-scanning is first recommended at six weeks and at three-monthly intervals thereafter until maximum regression of lymph nodes has occurred. Lymph node response may take several months in patients treated with anti-IL-6 mAbs.

Tables.

Therapy	Patients (n)	Response/m* (%)	No Response/m* (%)	Treatment Failure/m* (%)	Data Combined From References
All Therapies	344	281/461 (61)	180/461 (39)	163/367 (44)	11,21,32,33,39, supplementary appendix citations
Corticosteroid Monotherapy	117	53/114 (46)	61/114 (54)	62/115 (54)	22, 23, 44, supplementary appendix citations
Corticosteroid or Cytotoxic Chemotherapy (not distinguished)	19	12/19 (63)	7/19 (37)	NA	21
Cytotoxic Chemotherapy (any time used)	135	102/131 (78)	29/131 (22)	44/105 (42)	7, 22, 23, supplementary appendix citations
Anti-IL-6 mAb (without cytotoxic agent or rituximab)	147	88/144 (61)	56/144 (39)	32/100 (32)	7, 22, 23, 43, 44, supplementary appendix citations
Immunomodulator (without cytotoxic agent)	27	18/26 (69)	8/26 (31)	10/26 (38)	23, supplementary appendix citations
Other	16	8/13 (62)	5/13 (38)	12/15 (80)	23, supplementary appendix citations
No treatment/Follow-up Only	18	0/14 (0)	14/14 (100)	11/14 (79)	7, 22, 23, supplementary appendix citations

Table 1. iMCD Clinical Case Series of 344 patients. Literature review of published case reports, small series, and clinical trials were compiled to inform and substantiate the experience and opinion of the Working Group authors. Cytotoxic chemotherapy regimens described may include the use of rituximab. n = number of subjects treated in each treatment regimen category; m = total number of regimens evaluated (479); m* = number regimens assessed for stated outcome. Treatment failure was defined as disease progression while on treatment or insufficient response requiring additional treatments. The main series included in this analysis are referenced. A detailed breakdown of the data is provided in **Supplementary Appendix 1**. The TAFRO case reports are tabulated in the **Table 3**. MDACC= MD Anderson Cancer Cancer Center case series. Other includes: plasma exchange (n=4), radiation (n=2), plasma exchange +

31

corticosteroids (n=2), IVIg (n=2), Polymyxin B-immobilized fiber column direct hemoperfusion and cytokine absorption (n=1), allogeneic stem cell transplant. (n=1), Cimetidine (n=1), antibiotics (n=1), corticosteroids and etanercept (n=1), interferon-alpha (n=1).

Purpose	Tests
Inflammatory Response	CBC, Renal Function, Liver Function, CRP, ESR, Fibrinogen, Immunoglobulins & Free Light Chains, Albumin, Ferritin*
Histopathology	Hypervascular/ Mixed Cellularity/Plasmacytic Variant
Virologic Status	HIV Serology, HHV8 qPCR (peripheral blood), EBER (lymph node), LANA-1 (lymph node)
Cytokine Profile	IL6, VEGF, sIL2 Receptor[†]
Imaging	CT-PET or CT Neck, Chest, Abdomen, Pelvis
Bone Marrow Evaluation	MGUS, Myeloma, Reticulin Fibrosis
Immunology	ANA, Rheumatoid Factor
Organ Function	ECHO, Pulmonary Function

Table 2. Recommended Work-up of iMCD. Work-up should include excisional lymph node biopsy for histopathologic examination to confirm features consistent with iMCD, establish histopathologic variety, and to rule out EBV and HHV-8 infection by EBER and LANA-1 staining. Blood work is helpful to exclude HIV infection, autoimmune disorders and monoclonal gammopathy of undetermined significance (MGUS)/myeloma as well as measure inflammatory markers, determine organ function, and evaluate cytokines levels including IL-6 and VEGF. *Ferritin is measured as an acute phase reactant. [†]Soluble IL2

32

receptor marks T cell activation. CT- and CT-PET scanning help to visualize the extent of the disease.

Bone marrow examination can exclude a concomitant plasma cell dyscrasia and screen for megakaryocyte

hyperplasia and reticulin fibrosis often observed in TAFRO-iMCD. The diagnostic criteria have recently

been published.[23] Additional organ assessment may be needed in severe cases.

Therapy	Patients (n)	Response (%)	No Response (%)	Treatment Failure (%)
All Therapies	49	65/98 (66)	33/98 (34)	52/98 (53)
Corticosteroid Monotherapy	25	9/25 (36)	16/25 (64)	18/25 (72)
Cyclophosphamide-based cytotoxic chemotherapy	14	13/14 (93)	1/14 (7)	4/14 (29)
Rituximab with Cytotoxic Agent	1	1/1 (100)	0/1 (0)	0/1 (0)
Rituximab without Cytotoxic Agent	10	9/10 (90)	1/10 (10)	4/10 (40)
Cytotoxic Regimen (without Cyclophosphamide or Rituximab)	3	2/3 (67)	1/3 (33)	1/3 (33)
Tocilizumab with or without Steroids	20	15/20 (75)	5/20 (25)	10/20 (50)
Siltuximab with or without Steroids	1	1/1 (100)	0/1 (0)	1/1 (100)
Cyclosporine A (without Cytotoxic Agent)	8	6/8 (75)	2/8 (25)	2/8 (25)
Immunomodulators – Other than Cyclosporine A (without Cytotoxic Agent)	9	5/9 (56)	4/9 (44)	5/9 (56)
Other	7	4/7 (57)	3/7 (43)	7/7 (100)

Table 3. iMCD-TAFRO Cases. These were compiled from published case reports and small series. n =

number of subjects treated in each treatment regimen category, with a total of 98 regimens evaluated.

Other includes: plasma exchange (n=3), plasma exchange + corticosteroids (n=2), Polymyxin B-

immobilized fiber column direct hemoperfusion and cytokine absorption (n=1), allogeneic stem cell

transplant (n=1). Please refer to **Supplementary Appendix 1** for complete list of references.

Severe iMCD

- ECOG ≥ 2
- Stage IV renal dysfunction (eGFR < 30; Creatinine >3.0)
- Anasarca and/or ascites and/or pleural/pericardial effusion (effects of hypercytokinemia/low albumin)
- Hemoglobin ≤ 8.0g/dL
- Pulmonary involvement /interstitial pneumonitis w/dyspnea

Figure 1

Management of iMCD
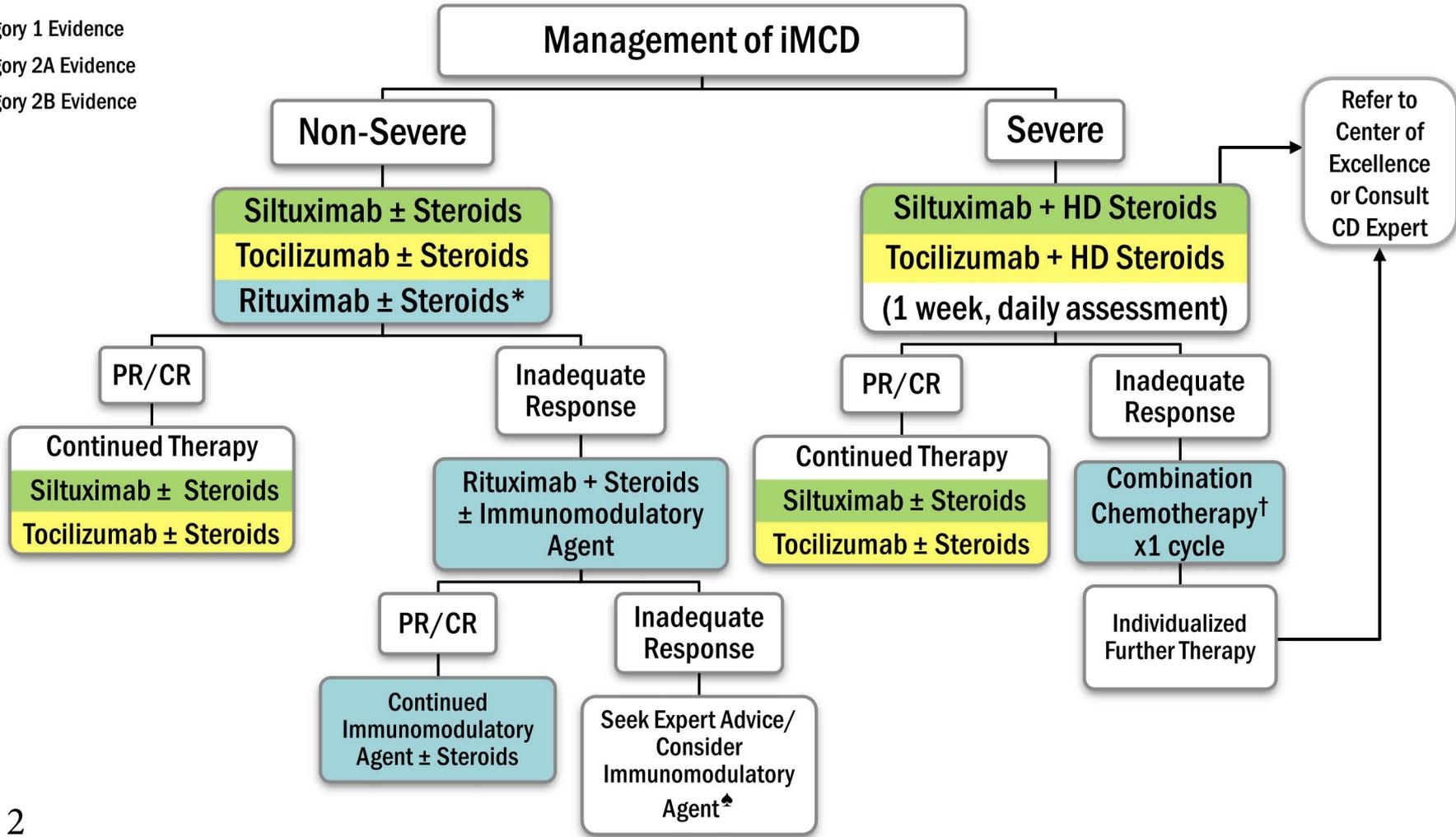
Category 1 Evidence
Category 2A Evidence
Category 2B Evidence

Non-Severe

Siltuximab ± Steroids
Tocilizumab ± Steroids
Rituximab ± Steroids*

PR/CR

Continued Therapy
Siltuximab ± Steroids
Tocilizumab ± Steroids

Inadequate Response

Rituximab + Steroids ± Immunomodulatory Agent

PR/CR

Continued Immunomodulatory Agent ± Steroids

Inadequate Response

Seek Expert Advice/ Consider Immunomodulatory Agent♠

Severe

Siltuximab + HD Steroids
Tocilizumab + HD Steroids
(1 week, daily assessment)

PR/CR

Continued Therapy
Siltuximab ± Steroids
Tocilizumab ± Steroids

Inadequate Response

Combination Chemotherapy† x1 cycle

Individualized Further Therapy

Refer to Center of Excellence or Consult CD Expert

Figure 2

Overall Response	Biochemical	Lymph Node	Symptoms
CR	Normal CRP, Hemoglobin, Albumin, GFR	CR	Normalization to baseline
PR	>50% improvement in all of CRP, Hemoglobin, Albumin, GFR	PR	Improvement in all 4 symptom categories, but not to baseline
SD	<50% improvement (or < 25% worsening) in all of CRP, Hemoglobin, Albumin, GFR	No PR or CR	Improvement in at least 1 (but not all) symptoms
PD	>25% worsening in any of CRP, Hemoglobin, Albumin, GFR	>25% increase	Any symptoms worse on ≥2 assessments

Symptom	Improvement Criteria
Fatigue	Decrease of ≥1 CTC grade point relative to baseline
Anorexia	Decrease of ≥1 CTC grade point relative to baseline
Fever	Decrease of ≥1°C relative to baseline
Weight	Increase of ≥5% relative to baseline

Figure 3