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Unmet Clinical Needs in the Management of Idiopathic Multicentric Castleman Disease: A Consensus-based Position Paper From an ad hoc Expert Panel

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ABSTRACT

Castleman disease describes a group of heterogeneous clinicopathological disorders now included in the tumor-like lesions with B-cell predominance of the World Health Organization classification. Managing idiopathic multicentric Castleman disease (iMCD) is challenging, because few systematic studies or comparative randomized clinical trials have been conducted. International, consensus evidence-based guidelines for iMCD were published in 2018, but gaps in the therapeutic options for difficult-to-treat patients, who do not respond to siltuximab and other conventional therapies, still exist. This article presents the results of group discussion among an *ad hoc* constituted Panel of Italian experts to identify and address unmet clinical needs (UCNs) in managing iMCD. Recommendations on the appropriateness of clinical decisions and proposals for new research concerning the identified UCNs were issued through formalized multiple-step procedures after a comprehensive analysis of the scientific literature. The following key UCNs were addressed: strengthening the diagnostic certainty in iMCD patients before planning first-line therapy; management of siltuximab therapy; choice and management of immune-modulating, or chemotherapy agents in patients resistant/intolerant to siltuximab therapy. While most of the conclusions reached by the Panel are consistent with the existing guidelines, some alternative therapeutic options were stressed, and the discussion contributed to bringing forth the issues that need further investigation. Hopefully, this comprehensive overview will improve the practice of iMCD and inform the design and implementation of new studies in the field.

INTRODUCTION

Castleman disease (CD) describes a group of heterogeneous hematologic disorders with peculiar histopathological features, now included in the World Health Organization category of tumor-like lesions with B-cell predominance.[1] CD is a rare disease with an estimated incidence and prevalence of 3.4 and 6.9 cases per million, respectively.[2] CD can present with unicentric or multicentric regions of lymph node enlargement.[3] While the unicentric CD is often asymptomatic or presents with mild symptoms,[3,4] multicentric CD (MCD) describes a group of polyclonal lymphoproliferative disorders characterized by intense episodic systemic inflammatory symptoms, such as fever, night sweats, malaise and weight loss, generalized lymphadenopathy,

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cytopenias, and multiorgan dysfunction.[3] MCD is further divided, based on the etiological driver, into human herpesvirus-8 (HHV-8)-associated,[5] often observed in immunosuppressed and/or HIV-positive patients,[6,7] MCD associated with Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal proteins, and Skin changes syndrome (POEMS),[8] and idiopathic MCD (iMCD) (Figure 1).[9] iMCD is often subclassified into iMCD-TAFRO, associated with Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis, Organomegaly, elevated C-reactive protein (CRP), and renal dysfunction,[10–12] and iMCD not otherwise specified (iMCD-NOS), which includes all presentations other than TAFRO, often characterized by thrombocytosis and hypergammaglobulinemia (Figure 1).[13]

Patients with iMCD are classified as severe when they show high-grade organ dysfunction and abnormalities in laboratory tests, such as very high CRP levels, marked hypoalbuminemia and thrombocytopenia with a poor performance status that requires critical care and risk of organ failure and death[14]; patients with iMCD-TAFRO often fall into this category, and specific diagnostic criteria for iMCD-TAFRO have been developed.[15] Severe iMCD accounts for about 10%–20% of all iMCD cases.[16,17] Nonsevere iMCD cases have no evidence of abnormal organ function. They may have a good performance status or be symptomatic due to an interleukin-6 (IL-6)-driven inflammatory response that impedes daily activities and may require hospitalization without intensive care. Management of iMCD is challenging due to its wide variety of phenotypes; furthermore, few systematic studies or comparative randomized clinical trials have been conducted focusing on iMCD. In 2018, an International Working Group (IWG) of experts was convened by the Castleman Disease Collaborative Network (CDCN) to establish guidelines for disease management based on published literature.[14] The anti-IL-6 monoclonal antibody siltuximab (or tocilizumab as an anti-IL-6 receptor if siltuximab is unavailable) was recommended with or without corticosteroids as the preferred first-line therapy for iMCD.[14] Recently, the British Society of Hematology recommended that severely symptomatic and critically ill patients should receive parenteral corticosteroids and anti-IL-6 signaling therapy.[18] In the most severe cases, adjuvant combination chemotherapy was recommended in patients not responding to siltuximab.[14]

The recommendations issued by the IWG and the British Society of Hematology were mostly based on consensus among experts. They were not fully comprehensive, leaving some gaps in diagnosis and therapy management that need to be filled, especially about treating patients intolerant or refractory to anti-IL-6 therapy. Consequently, many clinically relevant questions on iMCD management remain, and unmet clinical needs (UCNs) continue challenging the clinical practice of physicians caring for patients with iMCD. The certainty of the diagnosis of iMCD, a prerequisite for therapy planning, is a challenge in clinical experience, as the disease does not have specific features that could be distinguished from other diseases causing lymphadenopathies. Furthermore, the availability of anti-IL-6 therapy varies among countries: the choice of first-line therapy currently depends on the indication and access within the country. Finally, since the pathogenesis and biology of iMCD have not been conclusively elucidated and evidence on the best therapy and regimen to choose within the therapeutic armamentarium available for nonresponders to anti-IL-6 therapy is limited, there is a great need for discussion of the gaps to be filled and for comprehensive new clinical research.

Two CD research and treatment experts considered the above issues crucial for treating patients with systemic disease. For this reason, they decided to convene an expert group of Italian researchers and clinicians to foster the development of a position paper aimed at identifying UCNs in the management of iMCD patients and producing recommendations on the appropriateness of clinical decisions concerning the identified UCNs, as well as making proposals for new research aimed at improving iMCD care.

DESIGN AND METHODS

Two chairmen (PLZ and MP) appointed a 10 members expert panel from different Italian research institutions, selected according to the conceptual framework elements of the NIH Consensus Development Program,[19] hereafter called "the Panel." The panel comprised 6 hematologists, 2 allergists/immunologists, and 2 pathologists. All panelists were from different Italian referral centers for iMCD, including the Hematopathology Unit of the IRCCS Azienda Ospedaliero-Universitaria, the Policinico S. Orsola, and the Istituto di Ematologia Seràgnoli (Bologna); the Department of Molecular Medicine, the Division of Hematology, and the Center for the Study of Myelofibrosis of the Fondazione IRCCS Policlinico San Matteo (Pavia); the Unit of Immunology, Rheumatology, Allergy and Rare Diseases of IRCCS San Raffaele Scientific Institute (Milan); the Hematology Division of the University of Torino and the AOU "Città della Salute e della Scienza" (Torino); the Division of Hematology

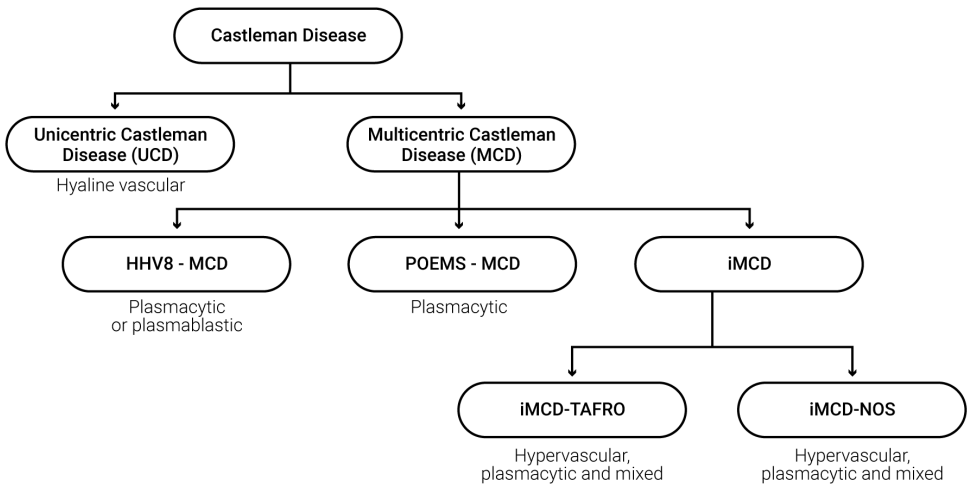

Figure 1. CD subtypes and lymph node histomorphology. CD = Castleman disease; HHV8 = human herpesvirus-8; iMCD = idiopathic multicentric Castleman disease; NOS = not otherwise specified; TAFRO = Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis, Organomegaly; POEMS = Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal proteins, and Skin changes syndrome.

of the AOU Policlinico "G. Rodolico-S. Marco" (Catania); the Unit of Hematology of the AORN "Sant'Anna e San Sebastiano" (Caserta); the Hematology Unit of the Sapienza University (Rome); the Department of Medicine-DIMED (Padua); and the Internal Medicine I, Ca' Foncello Hospital (Treviso). A clinician with expertise in clinical epidemiology assured the methodological appropriateness of the process. During an initial meeting, the Panel agreed on the areas of major concern in iMCD therapy by generating and rank-ordering key clinical questions using the criterion of clinical relevance, that is, impact on patient management and risk of inappropriateness, through a Delphi process.[20] The candidate key questions that ranked highest formed the set of UCNs of the present document. In the follow-up of the project, as for a consensus-based project, a nonsystematic literature search for English-language publications was performed. Electronic databases such as MEDLINE, EMBASE, and reviews, including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register, were used. We did not use restrictions for the publication date; databases were last searched on September 2022. Studies on pediatric cases of CD were not included. During a second meeting, the Panel examined the current knowledge regarding iMCD. Furthermore, 3 panelists drafted statements that addressed the identified UCNs. In a later phase of the project, the remaining panelists scored their agreement with these statements and provided suggestions for reformulation. The Expert Panel was convened to exploit this process phase, and 3 virtual consensus meetings were held. The meetings' overall goal was to reach a definite consensus over question-specific statements, for which disagreements occurred during a first-round postal phase. The nominal group technique was used, whereby participants were asked to comment in a round-robin fashion on their preliminary votes and then propose a new vote.[20]

RESULTS

UCN1: Strengthening the diagnostic certainty in patients diagnosed with iMCD

iMCD has no specific clinical features that can promptly be distinguished from other diseases causing reactive and/or neoplastic lymphadenopathies.[8,21,22] iMCD-TAFRO is hardly distinguishable from hemophagocytic lymphohistiocytosis and systemic lupus erythematosus, whereas iMCD-NOS is phenotypically similar to IgG4-related diseases, autoimmune lymphoproliferative syndromes, and Hodgkin lymphoma.[23] Patients with iMCD are also at high risk of developing lymphoproliferative disorders, which can greatly challenge the diagnosis of the disease.[16,24,25] These considerations claim the certainty of the diagnosis should be tenaciously sought in patients with suspected iMCD before planning the therapy. On the other hand, a strong suspicion of iMCD should result in immediate treatment, and delayed therapy while waiting for supporting information may negatively affect the prognosis, especially in the case of iMCD-TAFRO. Currently, there are no biomarkers to distinguish between iMCD-NOS and iMCD-TAFRO[26]; this should be a focus of future research (Table 1).

In 2017, a consensus paper included lymph node histomorphology among the major clinicopathological criteria required for diagnosing CD.[27] CD has been distinguished into 4 histological subtypes: hyaline vascular (HV), plasmacytic (PC), "mixed," with features intermediate between HV and PC subtypes, and plasmablastic.[16] Since, historically, the HV type has been attributed to unicentric CD cases, being present in about 90% of them,[28] the term "hypervascular" was proposed to identify HV morphology in multicentric cases.[28] The first 3 histologic types apply to all the clinical variants so far recognized, with the HHV-8-associated MCD and POEMS-associated MCD commonly showing a PC-type, the iMCD-TAFRO showing the HV12 subtype commonly, although PC and mixed subtypes have been observed,[29,30] and iMCD-NOS cases presenting with either subtype and high variability (Figure 1).[12,27–31] The plasmablastic histological type is exclusively associated with HHV-8-iMCD, and this subgroup has a very poor prognosis (Figure 1).[32,33]

Table 1

Hints for Future Research

Focus of Future Research to Improve Diagnosis	Focus of Future Research to Improve Therapy
Validation of existing techniques (Histology, BM biopsy, FDG-PET/CT) to discriminate iMCD from iMCD-mimicking conditions	Etiopathogenic mechanisms of iMCD
Identification and validation of specific biomarkers for iMCD	New therapeutic options for anti-IL-6 nonresponders
Identification and validation of biomarkers to discriminate between iMCD-TAFRO and iMCD-NOS	Response to anti-IL-6 mAb after successful chemotherapy in first-line anti-IL-6 nonresponders, despite increased pretreatment IL-6 production. Autologous and allogeneic stem cell transplantation is a supportive or last resort option.

BM = bone marrow; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography/computed tomography; IL-6 = interleukin-6; iMCD = idiopathic multicentric Castleman disease; TAFRO = Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis, Organomegaly; NOS = not otherwise specified.

According to the criteria of the above-mentioned CD variants, pathologists must be confident in typical CD histological marks and diagnostic pitfalls, particularly in differential diagnoses versus reactive or neoplastic conditions grounded on subtle, though not yet standardized histological features.[34,35]

Besides the distinctive histological features necessary to be recognized to strongly confirm the diagnosis of iMCD, the Panel argued about the contribution of further diagnostic features commonly found in iMCD to more accurate and timely diagnoses. In line with this purpose, the literature on bone marrow (BM) biopsy and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) results were analyzed to establish new biomarkers potentially useful for disease categorization and differential diagnosis.

Although BM evaluation is not included within the required criteria for iMCD diagnosis,[22] patients may rather frequently undergo BM biopsy as part of the diagnostic workup, especially when lymphoproliferative disorders or TAFRO-iMCD have been suspected: indeed, BM biopsy is useful to assess histopathological features, such as reticulin fibrosis, megakaryocytic hyperplasia, dysplastic changes, differences in cellularity and plasmacytosis, as reported in an examination of BM specimens from 24 iMCD patients with both iMCD-NOS and iMCD-TAFRO, where significantly more megakaryocytic hyperplasia was observed in the iMCD-TAFRO cases.[36] These findings were consistent with BM findings from 185 other published cases.[36] Even though these findings were relatively nonspecific for iMCD, as they can be found in several other infectious, malignant, and autoimmune diseases,[36] the Panel used this information to advise on BM biopsy in the iMCD differential diagnosis, in agreement with the guidance document published by Fajgenbaum et al[27] in 2017. Indeed, even if BM biopsy is not useful to diagnose iMCD per se, it may help to exclude lymphoma or myeloma (which, at times, can mimic iMCD) and to identify the variety of iMCD-TAFRO.[12,37–39]

FDG-PET/CT can enhance the specificity and sensitivity in identifying affected lymph nodes in iMCD patients thanks to its ability to collect structural and metabolic information.[21,40,41] For these reasons, FDG-PET/CT is recommended for iMCD diagnosis over CT: indeed, CT scan cannot detect normal-sized lymph nodes, does not take into account the metabolic activity, and cannot distinguish between reactive hyperplasia and pathological enlargement of lymph nodes.[14] Two studies reported a significantly higher lymph nodes maximum standardized uptake value (SUVmax) in multicentric versus unicentric CD,[42,43]

whereas the other 2 reported no significant differences.[44,45] Some studies indicate that FDG-PET/CT may be useful to discriminate among the CD subtypes[46] and between CD and lymphoma, but there is still no universal agreement.[44,47–52] In a more recent analysis, the highest SUVmax of lymph nodes per patient ranged from 2 to 19 with a mean value of 5.61 ± 3.12; therefore, most iMCD patients in the population demonstrated moderate FDG uptake with a mean "highest SUVmax" value.[40] Interestingly, a high SUVmax value was highlighted to induce suspicion of an alternative diagnosis (eg, lymphoma)[14] even if the only 2 patients in the study with the highest SUVmax of more than 10 did not develop lymphoma during the follow-up.[40] Despite the usefulness of FDG-PET/CT in discriminating between UCD and MCD being still controversial, the Panel included FDG-PET/CT examination in the discussion about excluding the alternative lymphoma diagnosis in iMCD patients.

The differential diagnosis between UCD and MCD is based more on imaging techniques such as CT scan and MRI[53] rather than histology because the histology of the HV subtype of UCD can be hard to distinguish from that of the hypervascular subtype of MCD[28]: distinctive features are the presence of nodal sinuses in MCD and dysplastic follicular dendritic cells in UCD.[27,28] The differential diagnosis of POEMS MCD from iMCD can also be challenging due to the variability of its clinical manifestations: 11%–30% of POEMS patients have iMCD-like histology,[54–57] and rare cases of iMCD can be associated with mild neuropathy.[58,59] Overall peripheral neuropathy occurs in approximately 27% of patients with CD.[57,58,60]

As regards differential diagnosis from iMCD-mimicking conditions, a full excisional lymph node biopsy should always be made because Castleman histologic features involve the entire lymph node, whereas changes induced by other conditions, such as lymphoma, are limited.[28]

UCN1: Recommendations and proposals

UCN1 recommendations are summarized in Table 2.

The Panel recommended that the certainty of the diagnosis should be strengthened before planning therapy in a patient diagnosed with iMCD; however, a delay in the initiation of therapy can strongly affect the prognosis in the most severe iMCD cases, so faster and reliable biomarkers and techniques to discriminate iMCD from mimicking pathologies should be investigated by future research efforts (Table 1).

While it can be challenging to identify the iMCD subtype with histology alone, a full excisional lymph node biopsy, overlooking needle and/or incisional samplings, can be discriminant toward HHV-8-MCD and other malignancies such as lymphoma. The Panel recommended that HHV-8 infection is peremptorily ruled out by latency-associated nuclear antigen-1 staining on lesional histological samples and plasma HHV-8 viral load analyses. The immunohistochemical exclusion of HHV-8-infected cells should be verified in the mantle zones and center of the follicles, as well as in the interfollicular area.

Pathologists must know that CD-like histopathological changes are not entirely specific and may occur in several reactive and neoplastic conditions. Alternative diagnoses include reactive lymphoid hyperplasia not otherwise specified, infectious lymphadenopathy, autoimmune diseases (ie, systemic lupus erythematosus, IgG4 disease), classic Hodgkin, and non-Hodgkin's lymphoma.

In the case of HV CD with prominent mantle zone expansion or predominant lymphoid component over the abnormal germinal centers and hypervascular interfollicular tissue, differential diagnosis with mantle cell lymphoma should be considered, particularly if the B cells are CD5 positive.[62] In mantle cell lymphoma, the germinal centers are composed of lymphoid elements rather than HV, with the interfollicular vascular component being only moderately increased.

Table 2

UCN in Diagnosis and Therapy

Potential Techniques to Strengthen Diagnosis Certainty	Endpoints to Analyze	Expected Outcome
Diagnosis		
Histology	Full excisional lymph node biopsy to analyze[61]: • Vascular proliferation and hyalinization of the vessel walls • Follicular and interfollicular changes • Vascularization of germinal centers • Mantle zone appearance • Plasma cells • LANA-1 staining	• Differential diagnosis from HHV-8 MCD and other malignancies (eg, mantle cell lymphoma): need for a skilled pathologist • A defined outline that allows maximal discrimination of iMCD mimics
BM biopsy	• Hypercellularity • Megakaryocytic atypia • Reticulin fibrosis • Plasmacytosis	Differential diagnosis: • Categorize TAFRO variant • Discriminate iMCD from myeloma or lymphoma
FDG-PET/CT lymph node imaging	Moderate FDG uptake (mean "highest SUVmax" value)	Differential diagnosis for lymphoma, solid cancer, and IgG4-mediated diseases
Cytometry and polymerase chain reaction assay	Immunoglobulin heavy/light chain gene rearrangement, B-cell clonality	Differential diagnosis with plasma cell diseases or B-cell lymphomas with plasmacellular differentiation

Recommended Therapeutic Options	Unmet Clinical Needs Still to be Addressed
Therapy	
Siltuximab 11 mg/kg every 3 weeks (as first-line therapy)	De-escalating treatment intensity to 11 mg/kg every 6 weeks in responding patients
Accelerated weekly dosing of siltuximab in most severe cases for 1 month	None
Adjunctive corticosteroids (in highly symptomatic iMCD) tailored to disease severity	Considering gradual corticosteroid dose tapering
Tocilizumab (if siltuximab is not available)	Performing studies to establish the optimal regimen for iMCD

BM = bone marrow; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography/computed tomography; HHV-8 = human herpesvirus-8; iMCD = idiopathic multicentric Castleman disease; LANA-1 = latency-associated nuclear antigen-1; SUVmax = maximum standardized uptake value; TAFRO = Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis, Organomegaly; UCN = unmet clinical need.

For CD with predominant plasma cellular features and monotypic light chain restriction, differential diagnosis with plasma cell diseases or B-cell lymphomas with plasmacellular differentiation should be considered (multiple myeloma, nodal plasmacytoma, lymphoplasmacytic lymphoma, or nodal marginal zone lymphoma). The immunoglobulin heavy/light chain gene rearrangement for B-cell clonality and cytometry should be performed for the differential diagnosis.

Although BM examination and FDG-PET/CT lymph nodes imaging are not listed among the iMCD diagnostic criteria, the Panel agreed on their investigational use in the diagnostic evaluation of iMCD.

In particular, BM examination may help categorize patients with a suspected TAFRO variant and differentiate BM involvement of myeloma or lymphoma from that of iMCD.

FDG-PET/CT may help differentiate between iMCD-mimicking conditions (lymphoma, solid cancer, and IgG4 disease) and identify ideal lymph nodes for biopsy; during treatment, it may also help to monitor the effectiveness of therapy.[46]

The Panel stated that further studies on larger series are warranted to indicate BM biopsy and/or FDG-PET/CT as diagnostic tools only in selected categories of patients.

UCN2: Management of siltuximab therapy

According to international treatment guidelines,[14] corticosteroid monotherapy is not recommended in iMCD because of a response failure rate of over 50% and nonnegligible side effects.[14] An overproduction of IL-6 by enlarged lymph nodes plays a pivotal role in the pathogenesis of a portion of iMCD cases, leading to an increased systemic inflammatory status.[63] Anti-IL-6 siltuximab therapy (11 mg/kg every 3 weeks) is recommended as first-line therapy, with corticosteroids as initial adjuvant therapy if necessary and with a dosing regimen tailored to the severity of symptoms.[14] Due to the side effects of corticosteroids, anti-IL-6 siltuximab therapy should be initiated early to discontinue steroids as soon as possible. Severe iMCD cases should be started immediately on siltuximab combined with high-dose corticosteroid therapy to prevent deterioration and death.[14] An aggressive treatment with weekly doses of siltuximab may be used for the 1st month of therapy; if a response is obtained, then siltuximab should be administered every 3 weeks indefinitely with gradual tapering of steroids.[14]

Recommendations on siltuximab use as first-line therapy of iMCD were derived from 2 clinical trials with a total of 116 participants.[64,65] Since no specific response criteria exist to evaluate iMCD, the 2 trials employed the Cheson criteria,[66] which were developed to evaluate lymphoproliferative disorders, to evaluate the lymph node size; Cheson criteria were modified to include assessment of cutaneous lesions caused by MCD, as previously described.[67] The phase 1 trial evaluated the clinical benefit response by assessing 6 iMCD-related clinical features,[64] whereas the phase 2 study employed a more complex 34 iMCD-related symptom score.[65]

The phase 1 single-arm trial performed by Kurzrock et al[64] included 37 patients with CD, 34 of which had iMCD. Siltuximab was administered at 3–12 mg/kg every 2 weeks.[64] Of 36 evaluable patients, complete response (CR), confirmed partial response (PR), and unconfirmed PR were reported by 1, 11, and 3 patients, respectively.[64] The confirmed overall response rate (ORR) was 33%.[64] Previously, an open-label, phase I dose-escalation trial on 23 patients showed that 18 patients had a clinical benefit, with 12 of them observing a reduction of lymph node size.[67] In the phase 1 trial performed by Kurzrock et al,[64] a total of 75% of the responders were administered the highest dose of 6 mg/kg/week. Grade ≥3 adverse events (AEs) occurred in 11% of patients, the most common being anemia.[64] An extension study of the phase 1 trial[64] demonstrated that siltuximab could be well tolerated and efficacious, maintaining disease control with minimal AEs even with continued use for a median of 5.1 years.[68] One patient with iMCD has been treated successfully with siltuximab as maintenance therapy for 15 years.[69] In a randomized controlled trial by van Rhee et al,[65] 79 patients with iMCD were included; 26 were assigned to placebo and 53 to intravenous siltuximab (11 mg/kg).[65] In the siltuximab group, 24 patients were newly diagnosed, and 29 were previously treated.[65] After a median follow-up of 422 (range: 55–1051) days, ORR was 34% versus 0% in the siltuximab and placebo groups.[65] Seventeen patients had a PR, and 1 had a CR on siltuximab.[65] The ORR was not significantly different for newly diagnosed diseases compared with previously treated diseases (33% vs 34%).[65] Grade ≥3 AEs were seen in 47% of cases in the siltuximab group versus 54% in the placebo group.[65] The most commonly reported grade ≥3 AEs in the siltuximab group were fatigue (9%) and night sweats (8%).[65] Siltuximab symptomatic response rates have been estimated at 60%, whereas the response rate in terms of durable symptoms control and reduction of lymph node size was 34%.[14,65]

A post hoc analysis of the phase II trial of siltuximab in iMCD[65] calculated the median time to a durable symptomatic response being 6.9 months. In contrast, the median time to achieve the reduction of lymph node size was 12.2 months and included only 49% of siltuximab-treated patients.[70] The delay between control of symptoms and reduction of lymph node size reflected the results obtained in previous trials and included in the consensus document[14]: it depends upon the mechanism of action of siltuximab that interferes with the growth signaling pathway for lymphocytes and plasma cells but does not have a direct cytotoxic effect.[14] For this reason, the response to anti-IL-6 therapy should not be measured on the bases of lymph node response but on the clinical symptoms and biochemical parameters of inflammation and organ function. These data suggest that siltuximab treatment can be safely prolonged for years maintaining clinical benefit, and suggest continuing siltuximab treatment after achieving symptom control because the reduction of lymph node size may require a longer duration of treatment, up to 2 years or more.[70]

After the approval of siltuximab, the Food and Drug Administration advocated for a composite response assessment for iMCD.[71] The consensus document published in 2018 established a composite endpoint to define response in iMCD, including 3 response categories: biochemical parameters of inflammatory response and organ function, lymph node size, and clinical symptoms.[14] Accordingly to these guidelines, CR requires normalization of all values, including the 4 important clinical symptoms defined by the National Cancer Institute Common Terminology Criteria of Adverse Events (version 4), whereas PR is achieved with a 50%–99% improvement in all laboratory values and improvement in the grades of all 4 symptoms, even without return to the baseline. The disease is defined as stable when a <50% improvement in all laboratory values or <25% worsening in any laboratory indicators occurs, and requirements for PR or progressive disease are not met, and as progressive when a >25% worsening in any laboratory marker occurs and any of the 4 symptoms worsens on ≥2 assessments 4 weeks apart.[14] In this composite assessment index, lymph node size is assessed using modified Cheson criteria as previously described.[67,72] The ORR results from the integration of the 3 response categories.[14]

Van Rhee et al[73] conducted a phase II extension study of patients from the first 2 trials where patients were categorized as having improved disease if 1 or more components of the disease, that is, hemoglobin, fatigue, anorexia, fever, weight, and size of the largest lymph node ameliorated with the others unchanged; stable disease was meant as no change in the considered outcomes, and disease progression was defined by a worsening in any component of the disease.[73] Sixty iMCD patients were recruited and given 11 mg/kg siltuximab infusion every 3 weeks.[73] The median duration of treatment was 5.5 years, including the previous trials.[73] Grade ≥3 AEs occurred in 60% of patients.[73] The most common grade ≥3 AE was hypertension (13%), followed by fatigue (8%) and nausea (7%).[73] Durable disease control was reported in 70% of patients for up to 6 years.[73] In this study, the dosing intervals of siltuximab were safely extended to 6 weeks in iMCD patients showing PR or CR for longer than 6 months, who accounted for 42% of iMCD patients[73]: only 1 patient of 25 (4%) returned to the original dosing due to suspected progression of the disease.[73]

Evaluating the results of the trials, the Panel argued about the decision to taper the dose of siltuximab in responding patients representing a UCN.

Given that durable responses to siltuximab with reduction of lymph node size have been observed in approximately one-third of the patients in the clinical trials[14] and few options exist for siltuximab nonresponders, the Panel also argued about the need for effective criteria for predicting the likelihood of response as an additional UCN. Biomarkers to predict whether a patient

will respond to siltuximab first-line treatment are fundamental: siltuximab therapeutic effect may take weeks to establish, but the window of time to treat the patient and decide whether to switch to chemotherapy is brief in most severe cases.

Data from the randomized controlled trial of siltuximab showed that all responders had either PC or mixed histopathological CD subtypes.[65] At the same time, none of the patients who achieved a durable response to siltuximab were classified as hypervascular subtypes by central review. Based on these data, the National Comprehensive Cancer Network issued guidance recommending first-line siltuximab therapy for iMCD, except for patients with hypervascular histopathology.[74] However, recent data from CDCN showed that histopathological subtypes are often assigned inconsistently among pathologists, with a concordance rate of only 23% in 3 pathology reviews at the local site, the central review, and a CDCN expert panel in the study.[75] Additionally, real-world data have shown that patients with severe iMCD, including TAFRO-iMCD and iMCD-NOS of the hypervascular subtype, may respond to anti-IL-6 therapy.[75–78] Therefore, there is currently insufficient evidence to guide treatment based solely on the iMCD histopathological subtype.

Morra et al[79] performed a secondary analysis of the results of the phase II trial by van Rhee et al[65] to find predictors of treatment response or failure among baseline laboratory parameters. In this study, the response was defined as lymph node and symptom control lasting more than 18 weeks.[79] CR was defined as the complete absence of symptoms and signs of the disease, whereas PR refers to a ≥50% decrease in symptoms and signs of disease and absence of treatment failure.[79] Nonresponders to siltuximab were patients experiencing a sustained increase in grade 2 or more symptoms persisting for at least 3 weeks or onset of any new disease-related symptoms grade 3 or higher or sustained deterioration in performance status, radiological progression, as measured by modified Cheson criteria[66,67] or needing to start any other therapy.[79] The study showed that patients with abnormal values of inflammatory-related parameters associated with IL-6-mediated processes (including CRP, fibrinogen, IgG, and hemoglobin) are good candidates for a beneficial response to siltuximab treatment. Although this model cannot be considered 100% sensitive due to the limited sample size and the exclusion of more severe iMCD cases, like TAFRO patients in which siltuximab has been shown effective.[76,77] Patients who do not respond to siltuximab probably have underlying mechanisms driving Castleman pathology unrelated to IL-6 signaling, which will be discussed later.[26,79–81] Analyzing a large cohort of iMCD samples, proteomic quantification of 1178 analytes was performed on the serum of 88 iMCD patients.[82] Unsupervised clustering of iMCD patients identified a subgroup with superior response to siltuximab, which was validated using a 7-analyte panel (apolipoprotein E, amphiregulin, serum amyloid P-component, inactivated complement C3b, immunoglobulin E, IL-6, and erythropoietin) in an independent cohort. Identifying and validating the subgroup with a superior response to siltuximab was considered the first validated predictive algorithm for response to siltuximab in iMCD. The same authors found that serum CXCL13 was higher in iMCD patients compared with healthy controls but did not differ between iMCD-TAFRO and iMCD-NOS.[83] CXCL13 showed potential to discriminate from a portion of pathologies with overlapping features as its serum levels were elevated compared with rheumatoid arthritis and HHV-8-MCD patients but not for patients with Hodgkin lymphoma.[83] Lymph nodes from patients with iMCD-TAFRO showed an increased expression of CXCL13 compared with lymph nodes of patients with iMCD-NOS.[83] A longitudinal analysis of sera samples of the phase 2 trial[68] was not able to identify pretreatment-specific biomarkers of siltuximab response, but identified CXCL13 as the only protein that was significantly different between responders and nonresponders at early and late time points, with a significant difference observed as early as after 8 days of treatment, in both the primary and validation cohorts.[83] The results indicate that a decrease in CXCL13 of 17% or more after starting siltuximab treatment is predictive of a good response to siltuximab.[83] Other 8 proteins besides CXCL13 were identified as differentially expressed after 8 days of treatment, and all of them except 1 were included in the 121 proteins found differentially expressed at late time points.[83] The importance of these results resides in the fact that serum indicators of response to siltuximab may exist as early as after 8 days of treatment. CXCL13 may be a candidate early biomarker to identify siltuximab response representing a turning point in iMCD therapy, because a rapid identification of nonresponders would allow switching immediately to chemotherapy with no delay and improved prognosis.

The systemic inflammatory state and cytokine storm associated with iMCD have provided the rationale for investigating the potential role of anti-CD20 antibody rituximab and immunomodulatory agent thalidomide as agents for first-line therapy. The use of rituximab and thalidomide is based on very limited evidence.[84,85] Rituximab and rituximab-based therapies have been reported to be inferior in terms of progression-free survival compared to siltuximab.[17] The consensus document indicates rituximab monotherapy as a first-line alternative to anti-IL-6 therapy for nonsevere iMCD without marked cytokine-dependent symptoms, where the advantage would be to avoid lifelong treatment,[14] but the evidence is scarce and based on limited data.[86–89] Evidence supporting its efficacy, when combined with chemotherapy, is more convincing, making it a viable option for patients with iMCD refractory to previous treatments.[84] Thalidomide as monotherapy reduced iMCD symptoms, but only a few studies are available[90,91] because it is more commonly used in combination with other immunomodulatory/immunosuppressive drugs. The results should be interpreted cautiously because of the lack of direct comparison with siltuximab in a randomized controlled trial.

In case siltuximab is not licensed or not readily available because it requires an individual funding request, especially for a severely ill patient needing intensive care support, tocilizumab may be used as first-line therapy. Tocilizumab is a monoclonal antibody that antagonizes the IL-6 receptor and is approved for treating iMCD in Japan. Evidence supporting the activity and safety of tocilizumab in iMCD was provided by an open-label, single-arm, nonrandomized Japanese study.[92] In 28 iMCD patients (2 with HHV-8 infection), a significant decrease (30%) was recorded in the mean short axis of swollen lymph nodes after 1 year of tocilizumab treatment.[92] Biochemical parameters (C-reactive protein, serum amyloid protein, fibrinogen, and erythrocyte sedimentation rate) improved significantly ($P < 0.001$) at week 6 of therapy.[92] Adverse reactions occurred in 27 (96%) patients, although no severe AE was observed.[92] The most common AEs were cold (57.1%), pruritus (21.4%), and malaise (21.4%).[92] A 5-year extension study investigated the long-term efficacy and safety of tocilizumab.[93] Of 35 MCD patients, 30 received tocilizumab for 5 years; 2.3 AEs were reported per patient/year, most of which were mild to moderate.[93] Reduction in lymph node size was sustained, and there was a significant improvement in pulmonary diffuse lymphoid hyperplasia.[93]

UCN2: Recommendations and proposals

UCN2 recommendations are summarized in Table 2.

The Panel agreed on the recommendations issued by the CDCN that siltuximab is the first-line therapy for iMCD patients.

The use and dose of accompanying corticosteroid therapy remain an individual choice that should be adjusted according to the severity of iMCD presentation.

The Panel recommended adjunctive corticosteroids (eg, methylprednisolone up to 2 mg/kg or equivalent) in highly

symptomatic patients with nonsevere iMCD and considered gradual dose tapering.

According to CDCN, in severe iMCD, siltuximab should be combined with a high-dose steroid regimen (eg, methylprednisolone 500 mg daily). For pharmacokinetic reasons, an accelerated, weekly dosing schedule of siltuximab might be used for 1 month, with a clinical reevaluation daily.

Current guidelines recommend siltuximab at the dose of 11 mg/kg every 3 weeks for an indefinite time with a high likelihood of maintaining disease response and a low risk of treatment-associated AEs.

The Panel emphasized the UCN to reduce the dose in responding patients, that is, de-escalating treatment intensity by switching siltuximab administration at 11 mg/kg every 6 weeks. The UCN could be addressed with retrospective registry-based clinical data on nonsevere iMCD cases who received 6-week siltuximab administrations compared with those with standard dosing schedules or prospective observational studies.

Despite contrasting evidence, the Panel suggested that a detailed assessment of histological characteristics at diagnosis may have some predictive potential and should be tested among the predictors of response but should be based on a defined outline conceived to maximize the potential to discriminate from iMCD mimics, performed by skilled pathologists and validated in a larger cohort of patients to avoid misinterpretation of histologic features. Further biopsies in these cases might provide information on both putative nodal changes therapy-related and CD morphologic features associated with no or partially responder patients.

The Panel agreed on claiming that the signature by proteomics represents a potential new clinical predictive tool for siltuximab therapy response and argued that an observational study is necessary to assess its value in predicting outcomes of siltuximab treatment.

The Panel agreed on recommending tocilizumab as a reasonable alternative therapy to siltuximab if the latter is not readily available. Compassionate use of the drug is advised according to regulatory requirements at the national level.

The recommended dose of tocilizumab is 8 mg/kg intravenously every 2 weeks. This therapeutic regimen has been adopted for systemic juvenile idiopathic arthritis. The Panel claimed that additional studies are required to identify the optimal dosage and timing of administration.

UCN 3: Choice and management of therapy in patients resistant/intolerant to siltuximab

About 50%–66% of patients with iMCD do not obtain or lose their response during first-line siltuximab therapy.[14,65,70] Refractory or relapsed iMCD presents a major clinical challenge because, despite many therapeutic options, limited clinical evidence is available to help select an appropriate regimen.[14] The consensus guidelines[27] suggest rituximab and corticosteroids with or without immunomodulatory/immunosuppressive agents, such as cyclosporine A, sirolimus, thalidomide, lenalidomide, bortezomib, anakinra, derivatives of retinoic acid, and IFN-α for nonsevere anti-IL-6 mAb refractory iMCD; this recommendation is largely based on case reports or series.[85,90,91,94–101] In particular, anakinra, which blocks the IL-1 beta receptor and NF-kB pathway, improved the conditions of an iMCD patient refractory to siltuximab and of a pediatric patient who partially responded to chemotherapy.[96,97] Accordingly, elevated levels of IL-1 beta and TNF-α have been reported in iMCD patients.[102,103] Response to immunomodulators/immunosuppressive cytotoxic therapy used in multiple myelomas, such as thalidomide, cyclophosphamide, prednisone, has been described in some patients with promising results and safety and is worthy of further investigation as an alternative therapy for anti-IL-6 nonresponders.[104] No clinical trial data are currently available on the optimal treatment in patients recognized as cases of TAFRO syndrome. Several therapies have been investigated in the case of reports, series, and retrospective cohorts, including immunosuppression with calcineurin inhibitors, anti-IL-6 agents, steroids, rituximab, thalidomide, and cytotoxic chemotherapy; response rates have varied greatly.[78,91,99,105–111] Among patients who show severe iMCD with TAFRO, cyclosporine A should be a useful therapy for anti-IL-6 mAb and chemotherapy-refractory cases to improve persistent ascites and thrombocytopenia.[112–116]

Sirolimus, an mTOR inhibitor, induced clinical benefit in 3 patients with anti-IL-6 refractory TAFRO-iMCD[117] and induced remission in a patient with TAFRO-iMCD with multiple relapses after repeated cycles of chemotherapy.[118] Increased PI3K/Akt/mTOR pathway activation has been observed in the lymph nodes of anti-IL-6 mAb refractory iMCD cases[119]: sirolimus treatment reduced CD8-positive T-cell activation and the VEGF-A levels achieving clinical remission in all cases.[117] A clinical trial on using sirolimus to treat iMCD is still ongoing (NCT03933904). mTOR is a promising target pathway also for the therapy of IL-6 inhibitor-refractory iMCD-NOS.[120]

IL-6-JAK-STAT3 signaling was reported to be also activated in siltuximab nonresponders,[82] suggesting that dysregulation of the IL-6–JAK–STAT3 signaling pathway may be involved in iMCD: pSTAT3 expression in the interfollicular areas of the lymph nodes in iMCD was found increased both in siltuximab responders and nonresponders.[82] Furthermore, JAK1/2 inhibition reversed the hyperresponse to IL-6 stimulation observed in the remission of peripheral blood mononuclear cells from iMCD patients.[119] These results suggest that ligands other than IL-6 may activate the JAK–STAT3 pathway and that JAK1/2 inhibitors may represent a valuable therapeutic strategy for siltuximab nonresponders.[26] IFN-I signaling seems involved in the JAK-mediated activation of mTOR in iMCD-TAFRO and may represent another pharmacological target.[121]

These agents should be considered over a second-line chemotherapy regimen, considering their lower toxicity and similar efficacy (56%, 75%, and 90% initial response for immunomodulators other than cyclosporine A, cyclosporine A, and rituximab, respectively).[14]

Overall, the response of patients with iMCD refractory to anti-IL-6 therapy strongly suggests the involvement of multiple chemokines/cytokines in iMCD pathology and requires further research on the etiopathogenetic mechanisms of iMCD (Table 1).[26]

Rituximab combined with cytotoxic chemotherapy should be reserved for the most severe settings of iMCD that did not respond to previous therapies, with very poor performance status and rapidly progressive disease, including those requiring intensive care units to control the cytokine storm and achieve rapid improvement in clinical status and biochemical parameters: indeed rituximab-chemotherapy showed a 78% response rate[14] but frequent relapses (42%) and considerable toxicity.[122,123]

In very severe patients, a lack of response to siltuximab after the 1st week of treatment would be an eligibility criterion for switching immediately to multiagent chemotherapy regimens as second-line therapy,[12,35,124,125] including those for lymphoma, for myeloma, or those containing etoposide for hemophagocytic lymphohistiocytosis.[14]

Autologous or allogenic stem cell transplantation has been employed successfully in POEMS iMCD cases,[60,126] whereas a few case reports on its use in non-POEMS MCD are available; however, in some studies, complete remissions with stem cell transplantation after multiple relapses and chemotherapy failure was also observed in HHV-8 negative patients,[127–129] suggesting that research efforts should be focused on exploring stem cell transplantation as a very last alternative when all the previous ones failed (Table 1).

In summary, the management of severe iMCD that fails anti-IL-6 mAbs and cytotoxic chemotherapy is not well defined and should be considered for each patient, taking into account

Table 3

Prediction of Nonresponders and Alternative Therapeutic Options

	Predictive Tool	Evidence for Predictive Value
Prediction of Nonresponders	Histology	Still insufficient evidence; need for a more detailed validation
	Proteomics signature	• A 7-analyte panel that identifies a subgroup with superior response to siltuximab. Needs to be validated by an observational study • CXCL13. Needs to be validated by an observational study
	Disease Presentation	**Therapeutic Options for Siltuximab Nonresponders**
Alternative Therapeutic Options for Siltuximab Nonresponders	Nonsevere iMCD	Immunomodulatory agents and rituximab, as monotherapy or in combination, with or without adjuvant corticosteroids
	Severe iMCD	Chemotherapy combination with rituximab
	Severe iMCD that fails or relapses after siltuximab and cytotoxic chemotherapy	Salvage multiagent chemotherapy is used for plasma cell malignancies

iMCD = idiopathic multicentric Castleman disease.

previous responses, comorbidities, performance status, and cytokine profile.

UCN3: Proposals of solution

UCN3 proposals are summarized in Table 3.

The heterogeneity of published data with different agents, small case numbers, lack of clinical trials, and other factors make it difficult to take any position on the treatment of patients who do not respond to anti-IL-6 therapy. Here, we reason on some aspects of the treatment of this subset of patients and provide some proposals of solutions that are aimed to be also suggestions for future investigation.

The Panel advised reconsidering the diagnosis of iMCD for patients who have not achieved a satisfactory response with siltuximab, ruling out a diagnosis of lymphoma or inflammatory disease; however, in the meantime, until fast and reliable biomarkers specific to iMCD diagnosis are available, most severe patients should be started on alternative therapeutic options immediately to avoid deterioration and risk of death.

In patients resistant/intolerant to siltuximab, the choice of therapy should be based on the preliminary distinction between nonsevere and severe diseases.

In nonsevere iMCD, immunomodulatory/immunosuppressive drugs, such as thalidomide, lenalidomide, sirolimus, rituximab, or anti-IL-1 receptor anakinra, should be considered before cytotoxic chemotherapy. A second-line salvage chemotherapy combination with rituximab (eg, R-CHOP/R-CVP/R-bortezomib, dexamethasone, and thalidomide [VTD]-PACE) should be considered in severe disease. In patients who have obtained a good response after rituximab, including chemotherapy, with elevated IL-6 levels before siltuximab therapy, maintenance treatment with siltuximab should be considered even if they did not respond during the acute phase because it cannot be excluded that after chemotherapy, the dysregulation of biochemical pathways other than IL-6 signaling, that were impeding siltuximab effect, may have resolved. Future research should investigate the response to anti-IL-6 mAb after chemotherapy in patients who did not respond in first-line treatment, despite having increased IL-6 levels (Table 1).

The management of severe iMCD that fails or relapses after siltuximab and cytotoxic chemotherapy (R-CHOP/R-CVP) is poorly defined. Salvage cytotoxic therapy, more commonly used in plasma cell malignancies, such as VTD, should also be taken into consideration, as suggested by the consensus guidelines.[14] Previous responses, comorbidities, performance status, and cytokine profile should be considered, and research should be focused on increasing the therapeutic armamentarium (Table 1).

CONCLUSION

The main aim of this endeavor is to optimize the care of patients with iMCD. Despite the paucity of high-level evidence on several important clinical issues, the Panel of experts reached a high degree of consensus. This consensus is a valid basis for the clinical implementation of recommendations and for developing new studies to guide therapeutic decisions.

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AUTHOR CONTRIBUTIONS

BG contributed to the literature research and wrote the first draft. All the other authors have critically contributed to the analysis and discussion of evidence and provided major intellectual input to the paper. All the authors have read and approved the final version of the paper before submission.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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REFERENCES

1. 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.
2. Mukherjee S, Martin R, Sande B, et al. Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy. *Blood Adv*. 2022;6:359–367.
3. Carbone A, Borok M, Damania B, et al. Castleman disease. *Nat Rev Dis Primers*. 2021;7:1–18.
4. Wong RSM. Unicentric Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:65–73.
5. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood*. 1995;86:1276–1280.
6. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. *Blood*. 2014;123:2924–2933.
7. Powles T, Stebbing J, Bazeos A, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann Oncol*. 2009;20:775–779.
8. Bonekamp D, Horton KM, Hruban RH, et al. Castleman disease: the great mimic. *Radiographics*. 2011;31:1793–1807.
9. van Rhee F, Greenway A, Stone K. Treatment of idiopathic Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:89–106.
10. 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;103:686–692.
11. Iwaki N, Sato Y, Takata K, et al. Atypical hyaline vascular-type castleman's disease with thrombocytopenia, anasarca, fever, and systemic lymphadenopathy. *J Clin Exp Hematop*. 2013;53:87–93.
12. 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.
13. Kojima M, Nakamura N, Tsukamoto N, et al. Clinical implications of idiopathic multicentric castleman disease among Japanese: a report of 28 cases. *Int J Surg Pathol*. 2008;16:391–398.
14. 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.
15. Nishimura Y, Fajgenbaum DC, Pierson SK, et al. Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. *Am J Hematol*. 2021;96:1241–1252.
16. Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. *Lancet Haematol*. 2016;3:e163–e175.
17. 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.
18. Lomas OC, Streetly M, Pratt G, et al. The management of Castleman disease. *Br J Haematol*. 2021;195:328–337.
19. Perry S, Wilkinson SL. The technology assessment and practice guidelines forum. A modified group judgment method. *Int J Technol Assess Health Care*. 1992;8:289–300.
20. Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning: a guide to nominal groups and Delphi process. Available at: https://sites.google.com/a/umn.edu/avandeven/publications/books/group-techniques-for-program-planning. Accessed October 5, 2022.
21. Madan R, Chen JH, Trotman-Dickenson B, et al. The spectrum of Castleman's disease: mimics, radiologic pathologic correlation and role of imaging in patient management. *Eur J Radiol*. 2012;81:123–131.
22. 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.
23. Fajgenbaum DC. Novel insights and therapeutic approaches in idiopathic multicentric Castleman disease. *Blood*. 2018;132:2323–2330.
24. Larroche C, Cacoub P, Soulier J, et al. Castleman's disease and lymphoma: report of eight cases in HIV-negative patients and literature review. *Am J Hematol*. 2002;69:119–126.
25. Peterson BA, Frizzera G. Multicentric Castleman's disease. *Semin Oncol*. 1993;20:636–647.
26. Sumiyoshi R, Koga T, Kawakami A. Candidate biomarkers for idiopathic multicentric Castleman disease. *J Clin Exp Hematop*. 2022;62:85–90.
27. 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.
28. Wu D, Lim MS, Jaffe ES. Pathology of Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:37–52.
29. Fujimoto S, Sakai T, Kawabata H, et al. Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? *Am J Hematol*. 2019;94:975–983.
30. Sato T, Ono Y, Matsushima J, et al. Histopathologic findings of TAFRO syndrome with immunohistochemical analysis of the kidney specimen: a case report. *Hum Pathol Case Rep*. 2021;23:200471.
31. Műzes G, Sipos F, Csomor J, et al. Multicentric Castleman's disease: a challenging diagnosis. *Pathol Oncol Res*. 2013;19:345–351.
32. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8–positive plasmablastic lymphoma. *Blood*. 2000;95:1406–1412.
33. Parravinci C, Corbellino M, Paulli M, et al. Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. *Am J Pathol*. 1997;151:1517–1522.
34. Wang W, Medeiros LJ. Castleman disease. *Surg Pathol Clin*. 2019;12:849–863.
35. Frizzera G. Castleman's disease and related disorders. *Semin Diagn Pathol*. 1988;5:346–364.
36. 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.
37. Kakutani T, Nunokawa T, Chinen N, et al. Treatment-resistant idiopathic multicentric Castleman disease with thrombocytopenia, anasarca, fever, reticulin fibrosis, renal dysfunction, and organomegaly managed with Janus kinase inhibitors: a case report. *Medicine (Baltimore)*. 2022;101:e32200e32200.
38. Ma WL, Zhang L, Zhu TN, et al. TAFRO syndrome – a specific subtype of Castleman's disease in China. *Chin Med J (Engl)*. 2018;131:1868–1870.
39. Iwasaki T, Mizusaki K, Masumoto M, et al. TAFRO syndrome with renal biopsy successfully treated with steroids and cyclosporine: a case report. *BMC Nephrol*. 2022;23:262.
40. Jiang Y, Hou G, Zhu Z, et al. 18F-FDG PET/CT imaging features of patients with multicentric Castleman disease. *Nucl Med Commun*. 2021;42:833–838.
41. Kligerman SJ, Auerbach A, Franks TJ, et al. Castleman disease of the thorax: clinical, radiologic, and pathologic correlation: from the radiologic pathology archives. *Radiographics*. 2016;36:1309–1332.
42. Kim JS, Lim ST, Jeong YJ, et al. F-18 FDG PET/CT for the characterization of Castleman's disease according to clinical subtype. *J Nucl Med*. 2010;51(suppl 2):1614–1614.
43. Lee ES, Paeng JC, Park CM, et al. Metabolic characteristics of Castleman disease on 18F-FDG PET in relation to clinical implication. *Clin Nucl Med*. 2013;38:339–342.
44. Rassouli N, Obmann VC, Sandhaus LM, et al. (18F)-FDG-PET/MRI of unicentric retroperitoneal Castleman disease in a pediatric patient. *Clin Imaging*. 2018;50:175–180.
45. O JH, Han EJ. F-18 FDG PET/CT findings of Castleman disease. *J Nucl Med*. 2018;59(suppl 1):19–19.
46. 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.
47. Hill AJ, Tirumani SH, Rosenthal MH, et al. Multimodality imaging and clinical features in Castleman disease: single institute experience in 30 patients. *Br J Radiol*. 2015;88:2014067020140670.
48. Ding Q, Zhang J, Yang L. (18)F-FDG PET/CT in multicentric Castleman disease: a case report. *Ann Transl Med*. 2016;4:58.
49. Fu Z, Zhang X, Fan Y, et al. Clinical value of 18F-FDG PET/CT in the management of Castleman's disease. *J Nucl Med*. 2013;54(suppl 2):1560–1560.
50. Murphy SP, Nathan MA, Karwal MW. FDG-PET appearance of pelvic Castleman's disease. *J Nucl Med*. 1997;38:1211–1212.
51. Elboga U, Narin Y, Urhan M, et al. FDG PET/CT appearance of multicentric Castleman's disease mimicking lymphoma. *Rev Esp Med Nucl Imagen Mol*. 2012;31:142–144.
52. Rossotti R, Moioli C, Schiantarelli C, et al. FDG-PET imaging in the diagnosis of HIV-associated multicentric Castleman disease: something is still missing. *Top Antivir Med*. 2012;20:116–118.
53. Zhao S, Wan Y, Huang Z, et al. Imaging and clinical features of Castleman disease. *Cancer Imaging*. 2019;19:53.
54. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101:2496–2506.

55. Li J, Zhou DB, Huang Z, et al. Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. *Ann Hematol*. 2011;90:819–826.
56. Soubrier MJ, Dubost JJ, Sauvezie BJ. POEMS syndrome: a study of 25 cases and a review of the literature. French Study Group on POEMS Syndrome. *Am J Med*. 1994;97:543–553.
57. Nakanishi T, Sobue I, Toyokura Y, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. *Neurology*. 1984;34:712–720.
58. Naddaf E, Dispenzieri A, Mandrekar J, et al. Clinical spectrum of Castleman disease-associated neuropathy. *Neurology*. 2016;87:2457–2462.
59. Mauermann ML. The peripheral neuropathies of POEMS syndrome and Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:153–163.
60. Lee YM, Choi YS, Kim JM. POEMS Syndrome: presented as idiopathic multicentric Castleman disease of plasma cell variant for eight years and dramatic treatment with siltuximab followed by autologous peripheral blood stem cell transplantation. *Diagnostics*. 2022;12:998.
61. Venkateswaran J, Balakrishna J. Available at: https://www.pathologyoutlines.com/topic/lymphnodescastleman.html. Accessed January 15, 2023.
62. Liu Q, Pittaluga S, Davies-Hill T, et al. Increased CD5 positive polyclonal B cells in Castleman disease: a diagnostic pitfall. *Histopathology*. 2013;63:8771–8880.
63. Yoshizaki K, Murayama S, Ito H, et al. The role of interleukin-6 in Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:23–36.
64. 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. *Clin Cancer Res*. 2013;19:3659–3670.
65. 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.
66. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–586.
67. 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;28:3701–3708.
68. 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;6:30408–30419.
69. Lang E, Sande B, Brodkin S, et al. Idiopathic multicentric Castleman disease treated with siltuximab for 15 years: a case report. *Ther Adv Hematol*. 2022;13:20406207221082550.
70. 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.
71. Deisseroth A, Ko CW, Nie L, et al. FDA approval: siltuximab for the treatment of patients with multicentric Castleman disease. *Clin Cancer Res*. 2015;21:950–954.
72. 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;17:1244.
73. 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.
74. Abramson JS. Diagnosis and management of Castleman disease. *J Natl Compr Canc Netw*. 2019;17:1417–1419.
75. 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.
76. Hawkins JM, Pillai V. TAFRO syndrome or Castleman-Kojima syndrome: a variant of multicentric Castleman disease. *Blood*. 2015;126:21632163.–216322163.
77. Behnia F, Elojeimy S, Matesan M, et al. Potential value of FDG PET-CT in diagnosis and follow-up of TAFRO syndrome. *Ann Hematol*. 2017;96:497–500.
78. Cordero L, Aguilar-Rodríguez F, Sandino J, Alonso M, Gutiérrez E. Siltuximab Monotherapy in Tafro Syndrome: A Case Report and Review of the Literature. *J Nephrol*. 2023 Jan 18. [Epub ahead of print].
79. Morra DE, Pierson SK, Shilling D, et al. Predictors of response to anti-IL6 monoclonal antibody therapy (siltuximab) in idiopathic multicentric Castleman disease: secondary analyses of phase II clinical trial data. *Br J Haematol*. 2019;184:232–241.
80. Wing A, Xu J, Meng W, et al. Transcriptome and unique cytokine microenvironment of Castleman disease. *Mod Pathol*. 2022;35:451–461.
81. Horna P, King RL, Jevremovic D, et al. The lymph node transcriptome of unicentric and idiopathic multicentric Castleman disease. *Haematologica*. 2023;108:207–218.
82. Pierson SK, Shenoy S, Oromendia AB, et al. Discovery and validation of a novel subgroup and therapeutic target in idiopathic multicentric Castleman disease. *Blood Adv*. 2021;5:3445–3456.
83. Pierson SK, Katz L, Williams R, et al. CXCL13 is a predictive biomarker in idiopathic multicentric Castleman disease. *Nat Commun*. 2022;13:7236.
84. 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.
85. Miltenyi Z, Toth J, Gonda A, et al. Successful immunomodulatory therapy in castleman disease with paraneoplastic pemphigus vulgaris. *Pathol Oncol Res*. 2009;15:375–381.
86. 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;78:302–305.
87. Ide M, Ogawa E, Kasagi K, et al. Successful treatment of multicentric Castleman's disease with bilateral orbital tumour using rituximab. *Br J Haematol*. 2003;121:818–819.
88. Ide M, Kawachi Y, Izumi Y, et al. Long-term remission in HIV-negative patients with multicentric Castleman's disease using rituximab. *Eur J Haematol*. 2006;76:119–123.
89. Mian H, Leber B. Mixed variant multicentric Castleman disease treated with rituximab: case report. *J Pediatr Hematol Oncol*. 2010;32:622622.
90. Starkey CR, Joste NE, Lee FC. Near-total resolution of multicentric Castleman disease by prolonged treatment with thalidomide. *Am J Hematol*. 2006;81:303–304.
91. 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 J*. 2015;5:e298.
92. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood*. 2005;106:2627–2632.
93. Nishimoto N, Honda O, Sumikawa H, et al. A long-term (5-Year) sustained efficacy of tocilizumab for multicentric Castleman's disease and the effect on pulmonary complications. *Blood*. 2007;110:646.
94. 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.
95. 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.
96. 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.
97. Galeotti C, Tran TA, Franchi-Abella S, et al. IL-1RA agonist (anakinra) in the treatment of multifocal castleman disease: case report. *J Pediatr Hematol Oncol*. 2008;30:920–924.
98. Lee FC, Merchant SH. Alleviation of systemic manifestations of multicentric Castleman's disease by thalidomide. *Am J Hematol*. 2003;73:48–53.
99. Tatekawa S, Umemura K, Fukuyama R, et al. Thalidomide for tocilizumab-resistant ascites with TAFRO syndrome. *Clin Case Rep*. 2015;3:472–478.
100. Yuan Z, Dun X, Li Y, et al. Treatment of multicentric Castleman's disease accompanying multiple myeloma with bortezomib: a case report. *J Hematol Oncol*. 2009;2:19.
101. Rieu P, Droz D, Gessain A, et al. Retinoic acid for treatment of multicentric Castleman's disease. *Lancet*. 1999;354:1262–1263.
102. Gherardi RK, Bélec L, Fromont G, et al. Elevated levels of interleukin-1 beta (IL-1 beta) and IL-6 in serum and increased production of IL-1 beta mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. *Blood*. 1994;83:2587–2593.
103. Nishi J, Arimura K, Utsunomiya A, et al. Expression of vascular endothelial growth factor in sera and lymph nodes of the plasma cell type of Castleman's disease. *Br J Haematol*. 1999;104:482–485.
104. 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.
105. Akiyama M, Kaneko Y, Takeuchi T. Tocilizumab for the treatment of TAFRO syndrome: a systematic literature review. *Ann Hematol*. 2020;99:2463–2475.

106. Hiramatsu S, Ohmura K, Tsuji H, et al. Successful treatment by rituximab in a patient with TAFRO syndrome with cardiomyopathy. *Nihon Rinsho Meneki Gakkai Kaishi*. 2016;39:64–71.
107. Shirai T, Onishi A, Waki D, et al. Successful treatment with tacrolimus in TAFRO syndrome: two case reports and literature review. *Medicine (Baltim)*. 2018;97:e11045e11045.
108. Yamagami K, Hanioka Y, Yao S, et al. A case of TAFRO syndrome maintained in remission for 5 years after discontinuation of tocilizumab. *Mod Rheumatol Case Rep*. 2023;7:205–210.
109. Williams C, Phillips A, Aggarwal V, et al. TAFRO syndrome and elusive diagnosis of idiopathic multicentric Castleman disease treated with empiric anti-interleukin-6 therapy. *CRO*. 2021;14:1359–1365.
110. Tanaka H, Bujo S, Itobayashi E, et al. TAFRO syndrome with a rapid fatal course despite corticosteroid and tocilizumab therapy. *J Hematopathol*. 2016;9:167–171.
111. Sozel H, Avsar E. TAFRO syndrome treated effectively with corticosteroids: a case report and review of the literature. *Indian J Nephrol*. 2022;32:168–171.
112. Takai K, Nikkuni K, Shibuya H, et al. [Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly]. *Rinsho Ketsueki*. 2010;51:320–325.
113. Takasawa N, Sekiguchi Y, Takahashi T, et al. A case of TAFRO syndrome, a variant of multicentric Castleman's disease, successfully treated with corticosteroid and cyclosporine A. *Mod Rheumatol*. 2019;29:198–202.
114. Yamaga Y, Tokuyama K, Kato T, et al. Successful treatment with cyclosporin a in tocilizumab-resistant TAFRO syndrome. *Intern Med*. 2016;55:185–190.
115. 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. *Tohoku J Exp Med*. 2015;236:289–295.
116. Inoue M, Ankou M, Hua J, et al. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporin A: a case report. *J Clin Exp Hematop*. 2013;53:95–99.
117. Fajgenbaum DC, Langan RA, Japp AS, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. *J Clin Invest*. 2019;129:4451–4463.
118. Fajgenbaum DC, Shilling D, Partridge HL, et al. Prolonged remission achieved in a relapsing idiopathic multicentric Castleman disease patient with a novel, targeted treatment approach. *Blood*. 2017;130(suppl 1):3593.
119. Arenas DJ, Floess K, Kobrin D, et al. Increased mTOR activation in idiopathic multicentric Castleman disease. *Blood*. 2020;135:1673–1684.
120. Sumiyoshi R, Koga T, Furukawa K, et al. A case of tocilizumab-refractory idiopathic multicentric Castleman's disease successfully treated with sirolimus. *Clin Immunol*. 2021;233:108887.
121. Pai RAL, Japp AS, Gonzalez M, et al. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease. *JCI Insight*. 2020;5:e135031.
122. 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;49:253–258.
123. Zhu SH, Yu YH, Zhang Y, et al. 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;30:492.
124. Herrada J, Cabanillas F, Rice L, et al. The clinical behavior of localized and multicentric Castleman disease. *Ann Intern Med*. 1998;128:657–662.
125. Weisenburger DD, Nathwani BN, Winberg CD, et al. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. *Hum Pathol*. 1985;16:162–172.
126. 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.
127. 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;94:1241–1243.
128. 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;93:677–680.
129. 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;68:171–176.