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ORIGINAL ARTICLE

Effectiveness of rituximab-containing treatment regimens in idiopathic multicentric Castleman disease

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Abstract

Human herpes virus type 8 (HHV-8)-negative, idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disease often involving constitutional symptoms, cytopenias, and multiple organ system dysfunction. In China, the majority of MCD cases are HHV-8 negative. Given that siltuximab, the only FDA-approved treatment for iMCD is not available in China; rituximab- and cyclophosphamide-containing regimens are often used in the treatment of Chinese iMCD patients. To evaluate the efficacy of rituximab in this rare and heterogeneous disease, clinical and pathological data from 27 cases of iMCD were retrospectively analyzed from two large medical centers in China. The novel diagnostic criteria for iMCD were applied, and POEMS syndrome, IgG4-related diseases, and follicular dendritic cell sarcomas cases were excluded from analyses. Total response rate of rituximab- and cyclophosphamide-containing regimens was 55.5%, with 33.3% (9/27) of the cases reaching CR and 22.2% (6/27) PR. In the 14 cases of R-R iMCD, total response rate was only 42.9% (CR 14.3% [2/14], PR 28.6% [4/14]). The 5-year OS of these 27 iMCD cases was 81% (95% CI 64–98; 27 total patients, 4 events, 23 censored) after receiving these regimens, but the 5-year PFS was 43% (95% CI 19–66; 25 total patients, 11 events, 14 censored). Thus, rituximab-based regimens should be considered for the treatment of iMCD patients when siltuximab is not available and potentially in siltuximab-refractory cases.

Keywords Idiopathic multicentric Castleman disease · Rituximab · Lymphoproliferative disease

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Introduction

Castleman disease (CD) is a rare lymphoproliferative disease, which was first described in 1956 by Dr. Benjamin Castleman [1]. CD can present with a unicentric or solitary enlarged lymph node (unicentric CD) or with multicentric lymphadenopathy that demonstrates histopathological features characteristic of CD. The heterogeneity of clinical manifestations and pathological features leads to difficulties in clinical diagnosis and treatment [2], especially among patients with multicentric CD (MCD). MCD cases often demonstrate constitutional symptoms, cytopenias, and multiple organ dysfunctions. Recent progress has been made for the diagnosis and management of MCD through recent efforts to define clinically meaningful subtypes [3]. Uncontrolled human herpes virus-8 (HHV-8) infection is the cause of approximately half of MCD cases in Western countries, particularly among immunocompromised individuals. HHV-8-negative MCD cases are considered to be "idiopathic" or iMCD when other possible etiologies such as concomitant POEMS syndrome

(polyneuropathy, organomegaly, endocrinopathy, M-protein, skin pigmentation), IgG4-related diseases (IgG4RDs), and follicular dendritic cell sarcomas (FDCS) have been ruled out [4]. The majority of MCD cases in China are HHV-8 negative [5, 6], but only about 70–80% of which can be classified as iMCD when POEMS syndrome, IgG4RDs, and FDCS are ruled out according to the recently published diagnostic criteria for iMCD by Fajgenbaum et al. [4].

The prognosis of iMCD is poor due to the paucity of effective treatment options in certain parts of the world. Due to the established pathological role of interleukin-6 (IL-6) in a portion of iMCD cases, the anti-IL-6 therapy siltuximab was developed and approved for the treatment of iMCD in many countries around the world based on a 34% response rate compared to 0% in the placebo arm [7]. However, siltuximab is not available in China, so the treatment strategy is different. Glucocorticoids and cyclophosphamide-based chemotherapy regimens with or without rituximab are the primary treatment options in China for iMCD, targeting inflammation, lymphoproliferation, and B cells, respectively [5, 6, 8, 9]. Although the efficacy of rituximab in HHV-8-associated MCD patients has been confirmed [10], its role in the treatment of iMCD patients has not been evaluated thoroughly. Most of the data available are from case reports or small case series. Recently, Yu et al. reported that rituximab or rituximab-based therapies were inferior to siltuximab in the treatment of iMCD at a large medical center in the USA in terms of complete remission (CR) and progression-free survival (PFS) [11]. However, rituximab was only administered in 21 cases, and they did not apply the international consensus diagnostic criteria for iMCD to determine included cases.

In this paper, we evaluated the efficacy of rituximab in the treatment of iMCD, using data from two large medical centers in China: The Peking University First Hospital (PUFH) and Peking Union Medical College Hospital (PUMCH). Here, the new diagnostic criteria for iMCD were applied, and the patients were further stratified based on their timing of rituximab-containing treatment regimens.

Materials and methods

Data collection

After obtaining approval from PUFH and PUMCH Internal Review Boards, 27 cases of iMCD with detailed clinical data were identified from the clinical and laboratory database of the two medical centers.

Patients screening

The procedure of patients screening was showed in Fig. 3 (supplement 1). These patients had been hospitalized from Jan 1995 to Nov 2016. The diagnosis of iMCD was based on clinical, laboratory, and pathological findings as defined by the international consensus diagnostic criteria [4]. HHV-8 status was determined by the immunohistochemical staining (IHC) of latency-associated nuclear antigen (LANA-1) in biopsy specimens from the MCD patients (Fig. 2).

Two-hundred thirty-eight cases of suspected MCD were screened for this study; 33 cases were excluded according to the major and minor criteria of the iMCD diagnostic consensus. Then, 21 cases of POEMS syndrome, 6 cases of systemic lupus erythematosus (SLE), 2 cases of IgG4-related diseases (IgG4RD), 5 cases of follicular dendritic cell sarcoma (FDCS), 2 non-Hodgkin lymphoma, 1 multiple myeloma, and 1 lung cancer were excluded. Thus, 165 cases of iMCDs were identified after 3 HHV8 patients were further excluded, in which 29 cases received rituximab-containing regimens. Finally, 27 cases with complete clinical data were analyzed in this study.

Although iMCD was thought to supersede a diagnosis of IgG4-related diseases (IgG4RD) in the international consensus diagnostic criteria [4], we excluded two cases of IgG4RD with definitive organ fibrosis. There were no patients with the newly described TAFRO syndrome (thrombocytopenia, anasarca/ascites, reticulin fibrosis in bone marrow, renal dysfunction, organomegaly) clinical subtype of iMCD in this cohort [12].

The clinical and laboratory data of the 27 cases of iMCD were extracted from the medical record databases of the two hospitals. The slides of diagnostic lymph nodes were re-evaluated by two experienced pathologists. The sizes of lymph nodes were determined from ultrasonic type B examinations and/or computed tomography (CT) scanning. According to the diagnostic criteria [4], iMCD was defined as having enlarged lymph nodes (> 1 cm in short-axis diameter) with characteristic CD-like histopathology in two or more lymph node stations.

Cheson criteria were employed to assess treatment response [13]. Chemotherapy naive (CN) iMCD patients were defined as those who never received any chemotherapeutic agents before rituximab- and/or cyclophosphamide-containing regimens were administered. Refractory-relapsed (R-R) iMCD cases were characterized as those who could not reach PR (no response, NR; or progressive disease, PD) after two cycles of chemotherapy, or relapsed more than 3 months after reaching CR or PR.

The treatment response and survival data were obtained through clinical follow-up. Follow-up information was gathered from review of visits or telephone records until the time of last follow-up or death. Follow-up was assessed until Dec 31, 2016.

Statistical analysis

Patient characteristics and treatment outcomes were summarized using descriptive statistics. Overall survival (OS) time was calculated from iMCD diagnosis until death or last

follow-up. Progression-free survival (PFS) was defined as the period from diagnosis to disease progression, relapse, or death. The Kaplan–Meier method was applied to calculate OS and PFS. The data was analyzed using SPSS 13.0.

Results

Demographic characteristics

The clinical and laboratory data of 27 patients with iMCD from PUFH (14 cases) and PUMCH (13 cases) are provided in Table 1. This cohort includes 19 men and 8 women, with a median age of 44 years (IQR 36 to 51). Approximately two thirds of the patients (17 cases) were classified as having the plasma cell histopathological subtype of iMCD while 5 cases had the hyaline vascular or hypervascular histopathological subtype of iMCD and 4 cases were mixed.

All 27 cases received more than two cycles of rituximab-containing regimens. Twenty-six of the cases included cyclophosphamide along with the rituximab-containing regimens. Thirteen patients were CN when they received the rituximab- and/or cyclophosphamide-containing regimens, while the other 14 patients were classified as R-R (Table 1). Approximately 2–6 cycles of cyclophosphamide-based chemotherapy regimens (e.g., CHOP) were administered in the R-R group before they received rituximab- and/or cyclophosphamide-containing chemotherapy (supplement Table 3).

Clinical features

The chief complaints on hospitalization for more than half (16) of the cases were lymphadenopathy. Eight patients presented with non-infectious fever. Seven patients presented with proteinuria and elevated serum creatinine, and six patients presented with skin rashes and/or plaques. The chief complaints of the remaining cases included edema, cough, diarrhea, and thrombocytopenia.

The most common clinical complications and laboratory abnormalities were renal injuries and cytopenias. The renal involvement varied from acute nephritic syndrome, nephrotic syndrome, and rapid progressive glomerulonephritis to chronic kidney injury. Seven patients with elevated serum creatinine were categorized as having chronic kidney disease (CKD) stages 3–5. Six patients had autoimmune hemolytic anemia and only one case had autoimmune thrombocytopenia. None of these cases met the criteria for systemic lupus erythematosus (SLE). One patient was found to have developed paraneoplastic pemphigus (PNP).

All patients were confirmed to have more than one enlarged lymph node after type B ultrasonic or computed tomography (CT) examinations. The majority of the biopsy sites were superficial cervical, supraclavicular, or inguinal region lymph nodes, but four cases were diagnosed from biopsies of mediastinal or retroperitoneal lymph nodes.

The clinical features necessary to meet the iMCD diagnostic criteria are summarized in Table 2. Eighty percent of patients (20/25) had elevated erythrocyte sedimentation rate (ESR) or C-reaction protein (CRP), 74.1% (20/27) had anemia, 55.6% (15/27) had hypoalbuminemia, 51.9% (14/27) had renal dysfunction (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) or proteinuria (total protein > 150 mg/100 ml), 29.6% (8/27) had constitutional symptoms, 29.6% (8/27) cases had thrombocytopenia, and 18.5% (5/27) had fluid accumulation. Large spleen and/or liver were confirmed in 9 out of 27 cases. Four in 27 cases had eruptive cherry

Table 1 General information of 27 cases iMCD patients received rituximab-based regimens

				Percentage (%)
1	Gender	Male	19	70.4
		Female	8	29.6
2	Age	44 years	(IQR 36 to 51)	
3	Pathological subtype	HV	5	18.5
		Mix	4	14.8
		PC	17	63.0
4	Clinical complications	With	18	66.7
		w/o	9	33.3
5	Treatment before rituximab	CN	13	48.2
		Refractory	9	33.3
		Relapsed	5	18.5
6	Response to rituximab-containing regimens	CR	9	33.3
		PR	6	22.2
		ND	7	25.9
		PD	5	18.5

HV hyaline vascular variant, *PC* plasmacytic variant PC, *Mix* mixed cellular variant, *CN* chemotherapy naïve

Table 2 Clinical characteristics of 27 cases iMCD patients received rituximab-based regimens

No.	Clinical features	Positive/total*	Percentage (%)
1	Elevated CRP (> 10 mg/L) or ESR (> 15 mm/h)	20/25*	80.0
2	Anemia (Hb < 12.5 g/dL for males, Hb < 11.5 g/dL for females)	20/27	77.8
3	Thrombocytopenia (platelet count < 150 k/μL) or thrombocytosis	8/27	29.6
4	Hypoalbuminemia (albumin < 3.5 g/dL)	15/27	55.6
5	Renal dysfunction (eGFR < 60 mL/min/1.73 m^2) or proteinuria (total protein > 150 mg/100 ml)	14/27	51.9
6	Polyclonal hypergammaglobulinemia (total gamma globulin or immunoglobulin G > 1700 mg/dL)	10/24*	41.7
7	Constitutional symptoms: night sweats, fever (> 38 °C), weight loss, or fatigue (> 2 CTCAE lymphoma score for B symptoms)	8/27	29.6
8	Large spleen and/or liver**	9/27	33.3
9	Fluid accumulation: edema, anasarca, ascites, or pleural effusion	5/27	18.5
10	Eruptive cherry hemangiomatosis or violaceous papules	4/27	14.8
11	Lymphocytic interstitial pneumonitis	0	0

*Total number less than 27 indicated some data were unavailable

**Based on the results of physical examination or USG-B

hemangiomatosis or violaceous papules. No lymphocytic interstitial pneumonitis was found in this group.

Clonality and transformations

Three of the 27 patients in this cohort had monoclonal immunoglobulins by immunofixation (IFE), suggesting a clonal B/plasma cell population, but these cases had no neurological impairment and the diagnostic criteria of POEMS syndrome was be met. For these three iMCD cases, transformation to malignancy was not observed during follow-up (27–59 months). However, two other cases of malignant transformations were documented: one was confirmed pathologically as Hodgkin lymphoma 27 months after the iMCD diagnosis. Mydelodysplastic syndrome refractory anemia with excess blasts (MDS-RAEB) and secondary acute myeloid leukemia was diagnosed in another iMCD case 22 months after iMCD diagnosis. Re-review of the initial diagnostic lymph node biopsy does not reveal any signs of the Hodgkin lymphoma or leukemia.

Treatments

All 27 iMCD cases received more than two doses of rituximab, with each dose being 375 mg/m^2 intravenously. The majority of the chemotherapy regimens were CHOP [cyclophosphamide, 500–750 mg/m^2 intravenous (IV) infusion, hydroxyl-doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV (maximum total dose 2 mg) on day 1 and prednisone orally on days 1 through 5 of a 21-day cycle] or COP (cyclophosphamide, vincristine, and prednisone), but TCP (thalidomide, cyclophosphamide, and prednisone) or TP (thalidomide and prednisone) were occasionally employed. One patient received 2 cycles of MINE (mitoxantrone, etoposide, and ifosfamide) before a rituximab-containing regimen. The dose, sequence, and regimen of drugs given varied across patients (Supplement Table 3). The side effects of the chemotherapy were acceptable; mild to moderate nausea, vomiting, and neutropenia were documented occasionally.

To evaluate the treatment response of rituximab-containing chemotherapeutic regimens, Cheson criteria [13] were employed. Total response rate of rituximab-containing regimens was 55.5%, with 33.3% (9/27) of the cases reaching CR and 22.2% (6/27) PR. Seven patients were classified as SD (25.9%) while the other five cases had PD (18.5%). In the 14 cases of R-R iMCD, total response rate was only 42.9% (CR 14.3% [2/14], PR 28.6% [4/14]), while both of the rates of SD and PD were 28.6% (4/14).

The 5-year OS of these 27 iMCD cases was 81% (95% CI 64–98; 27 total patients, 4 events, 23 censored) after receiving these regimens, but the 5-year PFS was 43% (95% CI 19–66; 25 total patients, 11 events, 14 censored) (Fig. 1a, b). The survival rate of CN iMCD cases was higher than that of the R-R cases (Fig. 1c), but the difference was not statistically significant ($P = 0.236$). The 5-year PFS of the R-R group was lower than that of the CN group (20 versus 76%), with P value of 0.078 (Fig. 1d).

Discussions

In mainland China, the majority of cases of MCD are HHV-8 negative (Fig. 2), but only about 70–80% of which can be

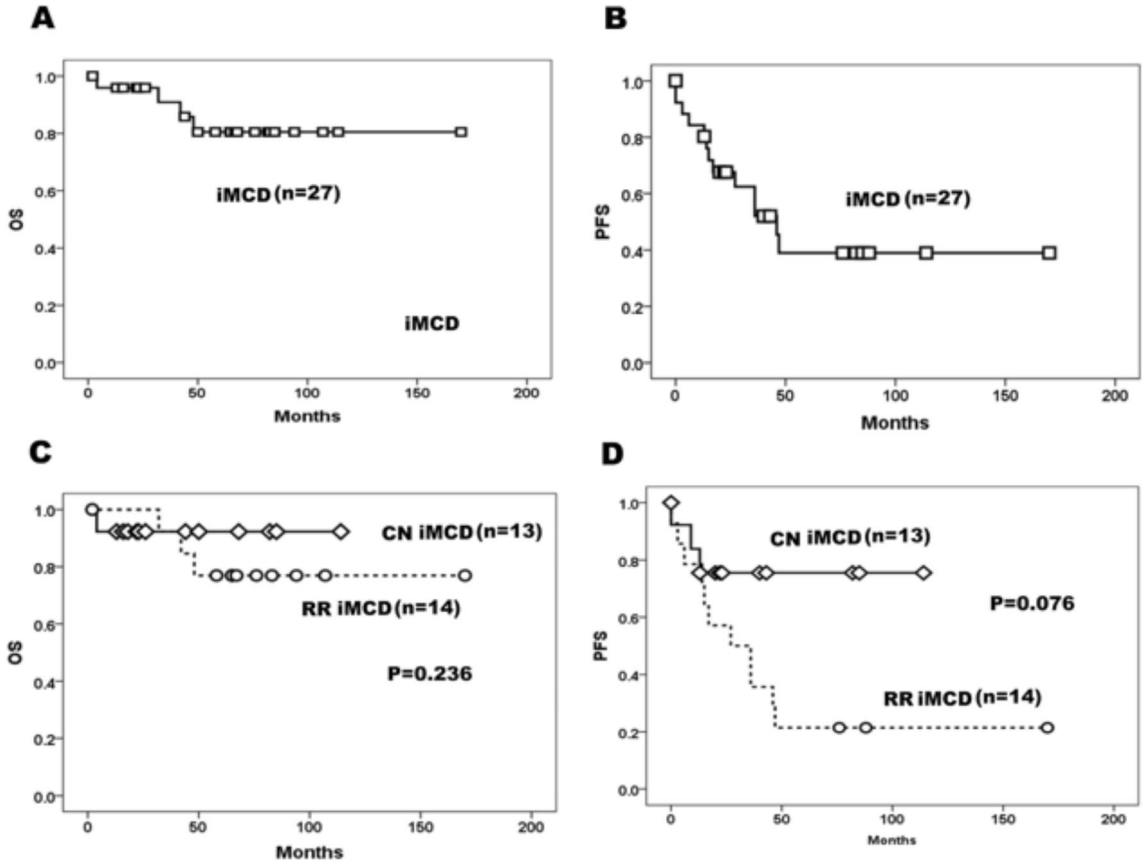

Fig. 1 Effect evaluation of the iMCD patients receiving rituximab-based chemotherapy. Kaplan–Meier plot of overall survival (**a**) and progression-free survival (**b**) of 27 cases of iMCD patients receiving rituximab-containing chemotherapeutic regimens. OS (**c**) and PFS (**d**) comparisons of chemotherapy naïve (CN, $n = 13$) and refractory-relapsed (R-R, $n = 14$) iMCD patients receiving rituximab-containing chemotherapeutic regimens

classified as "iMCD" according to the recently published diagnostic criteria for iMCD by Fajgenbaum et al. [4]. In this study, we excluded patients with confirmed autoimmune diseases, concomitant malignancies, POEMS syndrome, and IgG4RDs.

Previous studies have shown that certain clinical complications, such as PNP, are isolated to UCD [5, 6], but rare in iMCD. Herein, we found one of the 27 cases of iMCD to have PNP. The main complications were renal injuries and cytopenias. Clinical complications such as renal injuries affected the prognosis of iMCD cases, which has been demonstrated previously [5, 8, 11]. No sub-group analyses were further performed in the evaluation of treatment effect, partially due to small sample size.

The etiology of iMCD is unknown, and whether iMCD is a clonal disorder remains controversial. Currently, it is believed that UCD is driven by a clonal process, but that HHV-8-associated MCD and iMCD are not monoclonal. However, a study by Chang et al. refuted this hypothesis [14], and the question remains open. Two malignant transformations were observed in the cohort of iMCD patients: one to Hodgkin lymphoma and the other to MDS-RAEB and secondary AML. These two episodes were considered transformations, because the malignancies were diagnosed more than 1 year after iMCD, and there was no evidence of the malignancy on re-review of the previous diagnostic biopsies. Liu et al. found a threefold increased risk of malignancies among iMCD cases compared to age matched controls [15]. No transformation was observed during our follow-up (27–59 months) for the three iMCD cases with monoclonal immunoglobulins, indicating that monoclonality by sera IFE may not be a good technique to assess whether a monoclonal cell population underlies iMCD pathogenesis. New tools such as the immunoglobulin heavy chain (IgH) and T cell receptor (TCR) recombination and next-generation sequencing (NGS) should be employed to determine the clonality of the lymphocytes, plasma cells, and stromal cells. Given the origin of the lymphoproliferation in iMCD is still to be clarified, comparing the results of genomic sequencing of lymph node tissue with normal tissues (such as the hair roots or dermis biopsies) may identify somatic mutations underlying iMCD pathogenesis.

Siltuximab is the only drug to ever be studied in a randomized controlled trial in iMCD [7, 16]. IL-6 is believed to be the pathological driver of iMCD in at least a portion of patients. Alternative treatment approaches for patients refractory to

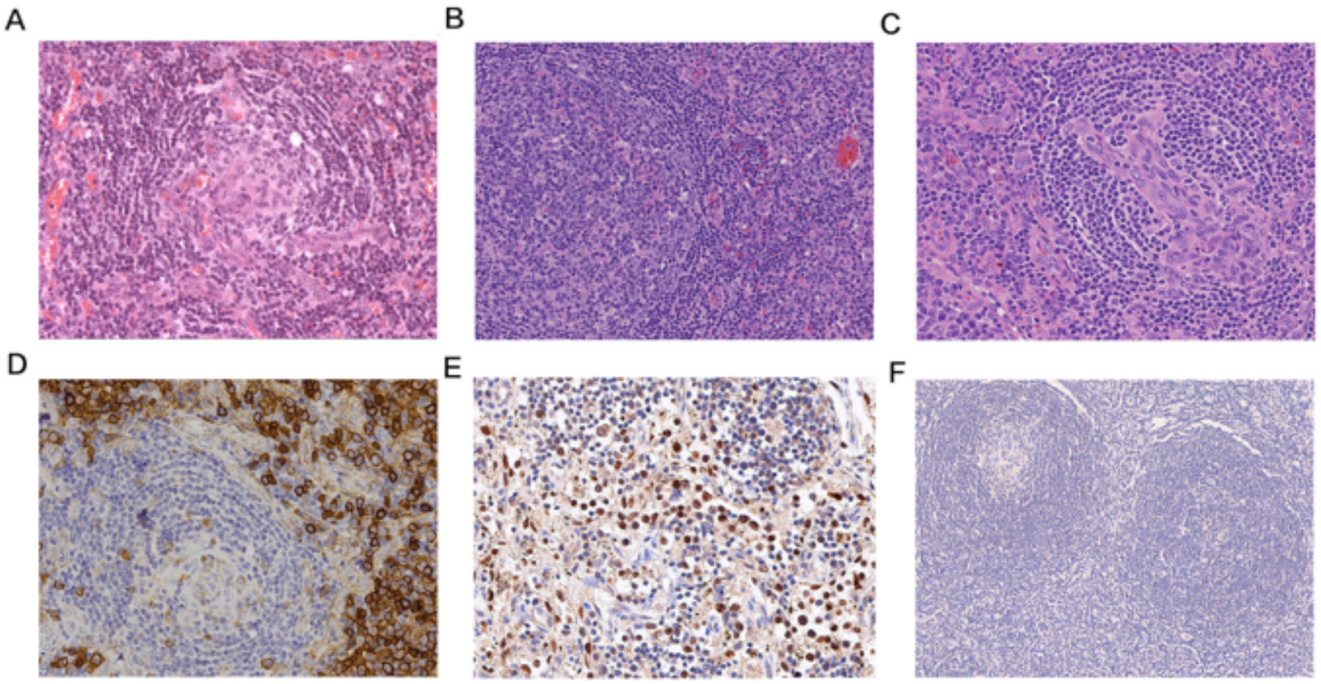

Fig. 2 Representative figures of three pathological subtypes. **a** Hyaline vascular variant (case #2, HE staining, × 200). **b** Plasmacytic variant (case #25, HE staining, × 200). **c** Mixed cellular variant (case #18, HE staining, × 200). **d** Immunohistochemistry staining anti-CD138 (case #18, × 200). **e** Positive control of HHV8 LANA1 staining (× 200). **f** Negative HHV8 LANA1 staining of a CD patient (case #2, × 100)

siltuximab or for patients in regions without access to siltuximab are urgently needed. Most of the evidences for efficacy of rituximab in iMCD come from case reports. Recently, Yu et al. reported that the PFS of iMCD patients receiving rituximab-containing regimens was not better than those receiving conventional chemotherapy, and the PFS of the siltuximab group was superior to the rituximab group ($P = 0.059$) [11]. Our previous study shown that 5-year OS of 44 cases of iMCD was 73% [5]. The 5-year OS among patients receiving rituximab-containing chemotherapeutic regimens was about 80%. Given that more than half of the iMCD patients in our cohort were refractory or relapsed with conventional chemotherapy not including rituximab, the effectiveness of rituximab-containing chemotherapeutic regimens seems acceptable. We did not directly compare the results of the patients treated with a rituximab-containing chemotherapeutic regimen with patients treated with conventional chemotherapy without rituximab, largely due to the heterogeneity of iMCD and different treatment starting points. Further case control studies or randomized prospective clinical trials are needed to elucidate this issue.

Although the OS and PFS of the CN group seemed better than those of the R-R group, no statistically significant difference was found (Fig. 1c, d). Due to the limited numbers of this group (27 cases), no definitive conclusions can be drawn. In summary, rituximab-based chemotherapeutic regimens should be considered for iMCD patients when siltuximab is not available, especially for patients refractory to conventional chemotherapy. However, the role of novel agents such as immunomodulators and kinase inhibitors in the treatment of R-R iMCD should also be further investigated.

There are two important limitations of this paper. The data was collected retrospectively; thus, there are obvious heterogeneities among the therapeutic regimens: the dose, the order, and the number of the cycles of the chemotherapy were not uniform. Secondly, no statistically significant conclusion can be drawn due to the small number of patients included. Given the importance of novel treatments for this deadly disease, multi-center prospective clinical trials are warranted.

In summary, although the rituximab-based regimens is not the first of choice, it should be considered for the treatment of iMCD patients when siltuximab is not available and potentially in siltuximab-refractory cases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Castleman B, Iverson L, Menendez VP (1956) Localized mediastinal lymph node hyperplasia resembling thymoma. Cancer 9(4): 822–830
2. Casper C (2005) The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 129(1):3–17. https://doi.org/10.1111/j.1365-2141.2004.05311.x

3. Fajgenbaum DC, van Rhee F, Nabel CS (2014) HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood 123(19):2924–2933. https://doi.org/10.1182/blood-2013-12-545087
4. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fosså A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS, Lim MS (2017) International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 129(12):1646–1657. https://doi.org/10.1182/blood-2016-10-746933
5. Dong Y, Wang M, Nong L, Wang L, Cen X, Liu W, Zhu S, Sun Y, Liang Z, Li Y, Ou J, Qiu Z, Ren H (2015) Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor. Br J Haematol 169(6):834–842. https://doi.org/10.1111/bjh.13378
6. Dong Y, Na J, Lv J, Wang R, Chen X, Li N, Ren H (2009) Clinical and laboratory characterization of a larger cohort of Castleman's diseases retrospectively collected from a single center. Leuk Lymphoma 50(8):1308–1317. https://doi.org/10.1080/10428190903060095.
7. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar R, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C (2014) Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 15(9):966–974. https://doi.org/10.1016/S1470-2045(14)70319-5
8. Xu D, Lv J, Dong Y, Wang S, Su T, Zhou F, Zou W, Zhao M, Zhang H (2012) Renal involvement in a large cohort of Chinese patients with Castleman disease. Nephrol Dial Transplant 27(S3):119–125. https://doi.org/10.1093/ndt/gfr245
9. Zhang L, Li Z, Cao X, Feng J, Zhong D, Wang S, Zhou D, Li J (2016) Clinical spectrum and survival analysis of 145 cases of HIV-negative Castleman's disease: renal function is an important prognostic factor. Sci Rep 6:23831. https://doi.org/10.1038/srep23831
10. Hoffmann C, Schmid H, Müller M, Teutsch C, van Lunzen J, Esser S, Wolf T, Wyen C, Sabranski M, Horst HA, Reuter S, Vogel M, Jäger H, Bogner J, Arasteh K (2011) Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. Blood 118(13):3499–3503. https://doi.org/10.1182/blood-2011-02-333633
11. Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J, Orlowski RZ, Neelapu S, Boddu PC, Akosile MA, Uldrick TS, Yarchoan R, Medeiros LJ, Li Y, Fajgenbaum DC, Young KH (2017) Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 129(12):1658–1668. https://doi.org/10.1182/blood-2016-11-748855
12. Iwaki N, Fajgenbaum DC, Nabel CS, Gion Y, Kondo E, Kawano M, Masunari T, Yoshida I, Moro H, Nikkuni K, Takai K, Matsue K, Kurosawa M, Hagihara M, Saito A, Okamoto M, Yokota K, Hiraiwa S, Nakamura N, Nakao S, Yoshino T, Sato Y (2016) Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol 91(2):220–226. https://doi.org/10.1002/ajh.24242
13. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-López A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17(4):1244. https://doi.org/10.1200/JCO.1999.17.4.1244
14. Chang KC, Wang YC, Hung LY, Huang WT, Tsou JH, M Jones D, Song HL, Yeh YM, Kao LY, Medeiros LJ (2014) Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. Mod Pathol 27(6):823–831. https://doi.org/10.1038/modpathol.2013.202
15. Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, Krymskaya VP, Kelleher D, Rubenstein AH, Fajgenbaum DC (2016) Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 3(4):e163–e175. https://doi.org/10.1016/S2352-3026(16)00006-5
16. Casper C, Chaturvedi S, Munshi N, Wong R, Qi M, Schaffer M, Bandekar R, Hall B, van de Velde H, Vermeulen J, Reddy M, van Rhee F (2015) 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. Clin Cancer Res 21(19):4294–4304. https://doi.org/10.1158/1078-0432.CCR-15-0134