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Continuous therapy in HHV-8 negative Multicentric Castleman Disease and prolonged progression-free survival

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Abstract
The optimal treatment endpoints and duration of continuous therapy for multicentric Castleman disease (MCD) remain controversial. We retrospectively analyzed data from 123 patients with Human Herpesvirus (HHV)-8 negative MCD. We demonstrated that continuous therapy significantly enhanced progression-free survival (PFS) in patients who achieved an optimal response after initial treatment. These findings underscore the critical role of continuous therapy in HHV-8 negative MCD. Further studies with larger cohorts are required to validate these findings.

Keywords Castleman Disease, HHV-8 negative Multicentric Castleman Disease, Continuous therapy

To the editor:

Multicentric Castleman disease (MCD) is a heterogeneous group of rare, systemic, progressive, and fatal diseases with lymphadenopathy in multiple nodes [1, 2]. An international consensus published in 2018 recommended anti-IL-6-based therapy as the first-line treatment for all patients with idiopathic MCD (iMCD) [3]. Zhang et al. also described a national trend of treatment options in China, with a shift from pulse chemotherapy to continuous approaches [4]. However, there is an ongoing debate about the "when to stop" issue: whether we should treat MCD with the goal of achieving a complete response (CR) and, once the desired response is achieved, whether the continuous therapy is still necessary [5–9]. This retrospective study aimed to evaluate the role and impact of continuous therapy in HHV-8 negative MCD.

A total of 123 patients diagnosed with HHV-8 negative MCD at the First Affiliated Hospital of Zhejiang University from 2015 to 2023 were identified, including 8 POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, and skin changes)-associated MCD (Figure S1). Patients had poor overall condition, with 67.5% (83/123) evaluated with an Eastern Cooperative Oncology Group (ECOG) score≥2 and 46.3% (57/123) classified with severe disease [10]. Patient baseline characteristics are summarized in Table 1 and Figure S2A. We categorized the regimens according to the year and first-line options (Figure S2 and Supplementary Data1). Between 2015 and 2019, R-CHOP or R-CHOP-like therapy (14.3%, 6/42), and

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Table 1 The clinical and laboratory characteristics of HHV-8 negative MCD patients

Characteristic	HHV-8 Negative MCD Patients ($n=123$)
Gender	
Male	75 (61.0%)
Female	48 (39.0%)
Age (years)	53.8 ± 13.8
ECOG (≥ 2)	83 (67.5%)
Severity	
Severe	57 (46.3%)
Mild	66 (53.7%)
Flare	68 (55.3%)
Pathological types	
HV	15 (12.2%)
PC	94 (76.4%)
MIX	14 (11.4%)
Systemic symptoms	
B symptoms	106 (86.2%)
Respiratory symptoms	59 (48.0%)
Digestive symptoms	32 (26.0%)
Skin involvement	38 (30.9%)
Elevated Scr (44–133 μmol/L)	1 (0.8%)
Pleural effusion and/or ascites	65 (52.8%)
	64 (52.0%)
Hepatomegaly	10(8.1%)
Splenomegaly	56(45.5%)
Hematologic Involvement	
RBC (3.5–5.5 × 10^9/L)	3.6 ± 1.0
Hb (115–150 g/L)	101.7 ± 28.9
WBC (3.5–9.5 × 10^9/L)	7.9 ± 5.5
PLT (100–300 × 10^9/L)	212.6 ± 136.6
Elevated D-Dimer (0–700 μg/L)	71 (57.7%)
Inflammatory markers	
Elevated CRP (0–8 mg/L)	89 (72.4%)
Elevated ESR (0–15 mm/h)	77 (62.6%)
Elevated Ferritin (7–323 μg/L)	57 (46.3%)
Cytokines	
Elevated IL-6 (0–5.3 pg/ml)	85 (69.1%)
Elevated IL-2 (0–5.71 pg/ml)	5 (4.1%)
Elevated IL-4 (0–3 pg/ml)	17 (13.8%)
Elevated IL-5 (0–3.1 pg/ml)	7 (5.7%)
Elevated IL-8 (0–20.6 pg/ml)	15 (12.2%)
Elevated IL-10 (0–4.91 pg/ml)	34 (27.6%)
Immunoglobulin	
Elevated IgG (860–1740 mg/L)	53 (43.1%)
Elevated IgA (100–420 mg/L)	38 (30.9%)
Elevated IgM (30–220 mg/L)	16 (13.0%)
Elevated IgG4 (0.03–2.01 g/L)	28 (22.8%)
Elevated LDH (120–150 U/L)	77 (62.6%)
Elevated AKP (35–100 U/L)	63 (51.2%)
Hypoalbuminemia	47 (38.2%)
Elevated Tbil (0–21 μmol/L)	12 (9.8%)

Abbreviations: AKP (alkline phosphatase); CRP (C-reactive protein); Dbil (direct bilirubin); ECOG (Eastern Cooperative Oncology Group); ESR (erythrocyte sedimentation rate); Hb (Hemoglobin); HV (hyaline-vascular); LDH (lactate dehydrogenase); MIX (mixed); PC (Plasma cell); PLT (platelet); RBC (red blood cell); Scr (Serum creatinine); WBC (white blood cell)

CHOP or CHOP-like therapy (23.8%, 10/42) were the most common regimen options. Since 2020, continuous treatment approaches have gradually become the first choice, utilizing IL-6 targeted therapy (17.9%, 14/78) and RVD/RCD/RD (30.8%, 24/78).

After a median follow-up of 22.7 months, the median overall survival (OS) [95% CI, Not Reached (NR) to NR] and PFS (95% CI, NR to NR) of all patients were not reached (Fig. 1A-B). Univariate and multivariate Cox regression analyses were performed to identify risk factors (Table S1-S2). Stratified by severity, patients with severe MCD had significantly worse OS ($p=0.03$) and PFS ($p=0.01$) than those in the mild MCD group (Figure S3A-B). Compared to patients without systemic symptoms, those experiencing a flare had worse OS ($p=0.006$), although the difference in PFS ($p=0.41$) was not statistically significant (Figure S3C-D). Subsequently, we stratified the patients with MCD based on different treatment endpoints. As shown in Fig. 1C-D, patients achieving the best response to CR, partial response (PR), or stable disease (SD) exhibited significantly longer OS than those who only progressed to progressive disease (PD) ($p=0.0001$). However, neither obtaining CR nor PR significantly extended both OS or PFS compared to patients with SD.

To assess the impact of sustained treatment on the prognosis of patients who achieved an optimal response after initial therapy, we designated patients who achieved PR or CR after 4–6 cycles of initial treatment as study participants. Patients who continued treatment for at least 3 months were classified into the continuous treatment (CT) group, while others were classified into the non-continuous treatment (NCT) group. Among the 54 patients who achieved their best response, 22 and 32 were classified into the CT and NCT groups, respectively. There were no significant differences in baseline characteristics (Tables S3). By the end of the follow-up period, 10 patients were still undergoing continuous treatment, 9 patients had ceased treatment and continued regular follow-up, 2 patients had relapsed, and 1 patient died from disease relapse following autologous hematopoietic stem cell transplantation (ASCT). Dynamic responses and continuous therapy options are presented in Fig. 1E. As depicted in Fig. 1F, continuous therapies were classified as rituximab-based therapy, thalidomide-based therapy, bortezomib-based therapy, immunomodulators, or glucocorticoids. Patients receiving continuous therapy had significantly improved PFS compared with those who did not receive maintenance therapy ($p=0.048$) (Fig. 1H). However, the OS was not significantly different between the two groups ($p=0.058$) (Fig. 1G).

In summary, although there are unavoidable challenges of potential bias, particularly in the context of such a rare disease, the significant improvement in PFS observed in

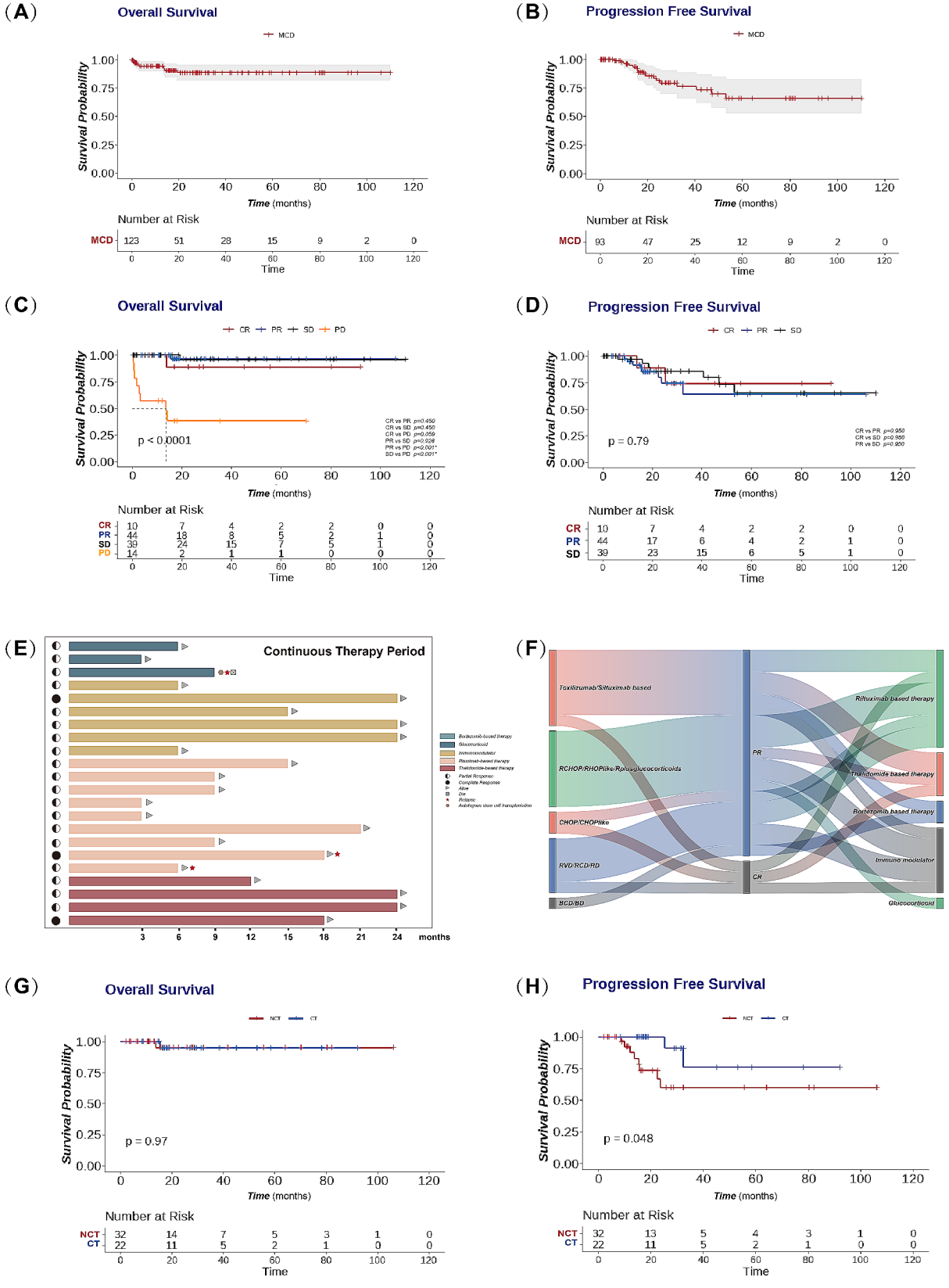

Fig. 1 (See legend on next page.)

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Fig. 1 (**A**) Overall Survival analysis of all MCD patients. (**B**) Progression Free Survival analysis of all MCD patients. (**C**) Subgroup Overall Survival analysis of MCD patients based on best treatment response. (**D**) Subgroup Progression Free Survival analysis of MCD patients based on best treatment response. (**E**) The Swimmer's plot shows the dynamic responses and different continuous therapies of MCD patients. The horizontal axis represents the duration of continuous therapy after patients achieved their best response. (**F**) Sankey plot illustrates the progression from the initial treatment regimen to the best response, and subsequently, to various continuous treatment options. (**G**) Subgroup Analysis of Overall Survival by Continuous Therapy. (**H**) Subgroup Analysis of Progression-Free Survival by Continuous Therapy

Abbreviations: MCD (multicentric Castleman disease); CR (Complete Response); PR (Partial Response); SD (stable disease); PD (progressive disease); BCD (bortezomib, cyclophosphamide, and dexamethasone); BD (bortezomib, and dexamethasone); CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); HV (hyaline vascular); RCD (rituximab, cyclophosphamide, dexamethasone); RD (rituximab, dexamethasone); R-CHOP/R plus glucocorticoids (R, rituximab); RVD (rituximab, bortezomib, dexamethasone); CT (Continuous Therapy);

the CT group reinforces the importance of continuous therapy as a crucial intervention for patients with HHV-8 negative MCD who have achieved an optimal response. However, the rarity of the disease and the heterogeneity of treatment approaches necessitate further research with larger cohorts and extended follow-up periods to validate our findings.

Abbreviations

ASCT	Autologous Hematopoietic Stem Cell Transplantation
CI	Confidence Interval
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
HHV-8	Human Herpesvirus 8
IL-6	Interleukin-6
iMCD	Idiopathic Multicentric Castleman Disease
MCD	Multicentric Castleman Disease
NCT	Non-Continuous Therapy
NR	Not Reached
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, and Skin changes
PR	Partial Response
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
RCD	Rituximab, Cyclophosphamide, and Dexamethasone
RVD	Rituximab, Bortezomib, and Dexamethasone
RD	Rituximab and Dexamethasone
SD	Stable Disease
TCP	Thalidomide, Cyclophosphamide, and Prednisone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01588-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Not applicable.

Author contributions
LSY designed and led the study. YL primarily participated in data collection, data analysis, manuscript writing, and figure preparation. XJY supervised the data analysis and manuscript writing. LSY, YL, HYT, HTM, and JJ contributed to the final manuscript supervision. All remaining authors were involved in the diagnosis and treatment of the disease, data collection, and approval of the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
Studies involving human participants were reviewed and approved by the independent Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University. The patients provided written informed consent to participate in the study.

Patient consent statement
All patients provided written informed consent.

Competing interests
The authors declare no competing interests.

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