Available online at www.blood-genomics.com

Blood and Genomics

2023, 7(2): 125−128

B & G

Brief Report

Efficacy of E-COD regimen in the treatment of HHV-8 negative multicentric Castleman disease

Xiaoyu Liu, Huihan Wang*

Department of Hematology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110035, China.

ABSTRACT

Castleman disease (CD) is a rare and heterogeneous disease whose treatment options and prognosis vary with clinical types. Multicentric Castleman disease (MCD) is characterized by poor prognosis, and effective treatment options are still being explored. This study aimed to determine whether the E-COD (E: etoposide 50 mg/m^2/d, d1–3; C: phosphoramide 750 mg/m^2, d1, d3; O: vincristine 2 mg, d1; D: dexamethasone 10 mg/d, d1–5) regimen is effective in treating human herpesvirus-8 (HHV-8)-negative MCD. A group of patients diagnosed with MCD at Shengjing Hospital of China Medical University were treated with E-COD regimen. The effectiveness evaluation was conducted after four treatment cycles and follow-up for survival. A total of 101 patients were included in this study from January 2003 to December 2021, of whom 29 patients had HHV-8 negative MCD subtype. Seven HHV-8 negative MCD patients received four courses of E-COD chemotherapy. The complete response, partial response, and stable disease were 14.3%, 71.4%, and 14.3%, respectively. The follow-up ended on June 1, 2021. Two patients died, and five patients survived, with a survival period ranging from 2 to 11 years. This study suggests that the E-COD regimen is a safe, efficient, and affordable therapy option for HHV-8 negative MCD patients.

Keywords: Castleman disease, multicentric Castleman disease, chemotherapy

INTRODUCTION

Castleman disease (CD), a rare lymphoproliferative illness also known as giant lymph node hyperplasia or angiolymphatic follicular hyperplasia, affects the lymph nodes[1–3]. According to the distribution of enlarged lymph nodes, CD is clinically divided into local Castleman disease (LCD) and multicentric Castleman disease (MCD). A deeper knowledge of CD has emerged in recent years, and therapeutic options have also drawn a lot of attention. LCD can be cured by surgical excision. Most of the patients have aggressive MCD, and some may develop into malignant lymphomas. Therefore, MCD patients urgently need relative treatments. However, treatment options are controversial because MCD rarely occurs. The characteristics of MCD are lymphoma and high inflammatory response, so a chemotherapy regimen based on lymphoma may be effective. T cell receptor (TCR) signaling may also play a role in the pathogenesis of MCD, which has been linked to an imbalance between the activation of T cells by antigens and their control. To establish a novel, efficient, and affordable program for the treatment of HHV-8 negative MCD, we added etoposide which inhibits the function of T cells to the CHOP (C:

*Corresponding to: Huihan Wang, Department of Hematology, Shengjing Hospital of China Medical University, No. 39 Huaxiang Road, Shenyang, Liaoning 110035, China. E-mail: wanghh@sj-hospital.org.

Conflict of interests: The authors declared no conflict of interests.

https://doi.org/10.46701/BG.2023022022037

Cyclophosphamide; H: Doxorubicin; O: Vincristine; P: Prednisone) protocol, and created an E-COD regimen for MCD patients.

SUBJECTS AND METHODS

Patients

Data from 101 patients diagnosed with CD at Shengjing Hospital of China Medical University were collected from January 2003 to December 2021. The study was approved by Shengjing Hospital's Ethics Committee (ethics number: 2017PS106J). As determined by the pathology, CD diagnoses can be classified as hyaline vascular (HV) type, plasma cell (PC) type, or mixed type[4]. The distribution of enlarged lymph nodes in CD is used to separate into LCD and MCD, in conjunction with physical examination, ultrasound, and imaging results.

Treatment

E-COD scheme: E: etoposide 50 mg/m^2/d, d1–3; C: phosphoramide 750 mg/m^2, d1, d3; O: vincristine 2 mg, d1; D: dexamethasone 10 mg/d, d1–5. A course of treatment comprises 21 days.

Follow-up and prognosis evaluation

This study adopted the CDCN 2017 version of the efficacy evaluation criteria, including the conclusion of the four treatment courses: complete remission (CR), partial remission (PR), stable disease (SD), and disease progression (PD)[3].

The patients were followed up by outpatient clinic and telephone calls, with the follow-up period ending on June 1, 2021. Then, the overall survival (OS) and progression-free survival (PFS) were calculated, respectively.

RESULTS

Patient characteristics

A total of 101 CD patients were divided into 72 (71.3%) LCD patients and 29 (28.7%) MCD patients. Seven MCD patients, including three men and four women (age range 15–63 years), underwent an E-COD regimen for at least four courses of chemotherapy. Their HIV and HHV-8 tests were all negative, and the pathological classification included four cases of PC type, one case of HV type, and two cases of mixed type. Anemia occurred in five individuals, fatigue, fever, night sweats, weight loss, and other systemic symptoms in two patients, and renal function impairment in four patients. Interleukin-6 (IL-6) levels were raised in four patients. five patients suffered hypoalbuminemia, three patients experienced edema and pleural ascites, three patients experienced rash and paraneoplastic pemphigus, and two patients experienced pulmonary interstitial alterations (***Table 1***).

Table 1 **Clinical characteristics of HHV-8 negative MCD patients**

N	Gender	Age	Histological feature	Symptom/ Fatigue	ECOG	IL-6 (0–7 pg/mL)	CRP (0–8 mg/L)	HGB (110–150 g/L)	eGFR (mL/min/1.73 m^2)	ALB (35–53 g/L)	Edema/ Pleural effusion	Skin lesion/ Paraneoplastic pemphigus	Pulmonary interstitial changes
1	M	48	PC	√	2	4.08	32.3	110	137.36	37	-	-	-
2	M	15	HV	√	2	31.2	31.6	91	29.7	9	√	√	-
3	F	60	PC	√	2	108.3	15.3	74	20.1	11	√	√	√
4	F	36	PC	√	1	6.9	15.6	129	131	35	-	-	-
5	M	63	MIX	√	1	16.7	6.9	46	100	5	-	-	√
6	F	29	MIX	-	1	69.0	16.2	31	117	9	√	√	-
7	F	54	PC	-	1	5.4	2.0	65	90.2	20	-	-	-

HHV-8: human herpesvirus-8; MCD: multicentric Castleman disease; ECOG: Eastern Cooperative Oncology Group; IL-6: interleukin-6; CRP: C-reactive protein; HGB: hemoglobin; eGFR: estimated glomerular filtration rate; ALB: albumin; PC: plasma cell; HV: hyaline-vascular; MIX: mixed.

Response and prognosis

Seven patients received four courses of E-COD chemotherapy. The CR, PR, and SD rates were 14.3%, 71.4%, and 14.3%, respectively. The overall response rate (CR + PR) reached 85.7%. Two patients died, and five patients survived during the follow-up period, with a survival period ranging from 2 to 11 years (***Table 2***). Case 5 died of interstitial lung disease and respiratory failure and case 6 died of significant effusion and heart failure. Patients 1, 4, and 7 achieved remission after a long-term follow-up period. Cases 2 and 3 remained stable in terms of disease during the three-year follow-up period. However, the follow-up time was still short.

Table 2 **Response and prognosis of E-COD regimen to treat HHV-8 negative MCD**

N	Biochemical efficacy	Lymph nodes (Cheson)	Symptoms improved	PFS (years)	OS (years)	Survival
1	CR	PR	CR	10	11	alive
2	CR	PR	CR	1	2	alive
3	PR	PR	CR	1	3	alive
4	CR	PR	CR	6	7	alive
5	PR	SD	PR	1	2	dead
6	PR	PR	PR	2	3	dead
7	CR	CR	CR	9	10	alive

E-COD: (E: etoposide; C: phosphoramide; O: vincristine; D: dexamethasone); HHV-8: human herpesvirus-8; MCD: multicentric Castleman disease; PFS: progression-free survival; OS: overall survival; CR: complete remission; PR: partial remission; SD: stable disease.

DISCUSSION

The prognosis and treatment choices for CD vary with clinical and pathological subtypes[5–7]. The prognosis of idiopathic MCD (iMCD) is poor, with reported 5-year survival rates ranging from 51% to 77%[8]. According to its etiology and clinical characteristics, MCD is further divided into HHV-8-related MCD, POEMS (P: polyneuropathy; O: organomegaly; E: endocrinopathy; M: monoclonal protein; S: skin changes)-related MCD, and iMCD, the latter being of unknown etiology that is not related to POEMS syndrome.

It is generally believed that MCD should be treated with systemic chemotherapy. However, it is challenging to establish a uniform and regular regimen as CD only occurs in a small percentage of instances. In the past, the COP (C: cyclophosphamide; O: vincristine; P: prednisone) or CHOP regimen was selected for treating CD. The CHOP regimen, based on the concept that CD is a lymphoproliferative disorder, includes glucocorticoids and has shown success in reducing the growth of lymph nodes. Zou *et al*. reported that enlarged lymph nodes disappeared after 6–8 courses of COP or CHOP chemotherapy in three patients with MCD[9]. The lymphocytes, particularly PC-type of MCD, were also found to express increased CD20, which provides a theoretical justification for the use of CD20 monoclonal antibodies[10]. In addition, studies have shown that excessive secretion of IL-6 and immune disorders were closely related to the pathogenesis of CD[11]. It is advised to treat CD using an anti-IL-6 antibody or anti-IL-6 receptor antibody[12]. However, it is still unclear whether elevated IL-6 levels are the cause or the result of CD. Therefore, more research is needed to determine whether the application of anti-IL-6 antibodies or anti-IL-6 receptor antibodies can merely treat disease symptoms or provide a cure. Some studies have shown that the pathogenesis of CD was related to viral infections such as HIV or HHV-8[13]. However, the prevalence of HIV and HHV-8 in CD varies between Western and Asian nations, and the majority of CD cases in China are not associated with either HIV or HHV-8 infection. Since 2003, we investigated 101 CD patients and found no cases of co-infection with HIV. However, the long-term prognosis after treatment with targeted therapy medications remains poor.

Etoposide, a T-cell activity inhibitor, was added to the E-COD treatment and used in the current study. The results, from a total of 7 patients who received E-COD chemotherapy, revealed that the treatment's overall response rate was 85.7%. Etoposide is an antitumor agent commonly used as an apoptosis inducer, which stops the cell cycle process and inhibits the proliferation of tumor cells. It is mainly used in the treatment of malignant lymphoma, malignant germinoma, leukemia, neuroblastoma, rhabdomyosar-coma, ovarian cancer, lung cancer, gastric cancer, and esophageal cancer. Hemophagocytic lymphohistio-cytosis (HLH) is a severe and sometimes fatal inflammatory state caused by abnormal immune regulation. It reduces the production of excess proinflammatory cytokines by selective ablation of over-activated T cells and inhibition of mononuclear macrophage activation[14]. As MCD is a type of CD with severe inflammatory response, etoposide was added to explore its potential in inhibiting the inflammatory response and treating MCD. This study suggests that the E-COD regimen is a safe, efficient, and affordable therapy option for HHV-8 negative MCD patients.

Another clinical feature of MCD is renal insufficiency; therefore, renal function is an important prognostic factor for survival[15–16]. Impaired renal function leads to decreased etoposide clearance, resulting in increased systemic exposure and more severe myelotoxicity. Therefore, a 30% dose reduction was recommended for patients with renal

insufficiency. Hematotoxicity was more pronounced in patients with hypoalbuminemia concentrations (<35 g/L). Due to reduced protein binding, the proportion of free drugs in this group increased, and a dose reduction of approximately 30% to 40% was required[17]. The E-COD regimen is an effective and economical treatment for relieving MCD. MCD is between benign and malignant, with a high inflammatory response and a tendency to reoccur, despite some advancements in systemic chemotherapy and molecular targeted therapy. To address concerns (when to begin treatment; how many sessions of treatment are necessary; and whether systemic chemotherapy can reduce symptoms while extending OS), more extensive large-scale evaluation and long-term surveillance are required.

Acknowledgments

We would like to express our immense gratitude to all the physicians in the Hematology Department of Shengjing Hospital of China Medical University for their support.

References

[1] Yu L, Shi M, Cai Q, et al. A novel predictive model for idiopathic multicentric Castleman disease: the internatiman disease consortium study[J]. *Oncologist*, 2020, 25(11): 963−973.

[2] van Rhee F, Oksenhendler E, Srkalovic G, et al. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease[J]. *Blood Adv*, 2020, 4(23): 6039−6050.

[3] van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease[J]. *Blood*, 2018, 132(20): 2115−2124.

[4] Frizzera G. Castleman's disease and related disorders[J]. *Semin Diagn Pathol*, 1988, 5(4): 346−364

[5] Zhang X, Rao H, Xu X, et al. Clinical characteristics and outcomes of Castleman disease: a multicenter study of 185 Chinese patients[J]. *Cancer Sci*, 2018, 109(1): 199−206.

[6] Dong Y, Wang M, Nong L, et al. Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor[J]. *Br J Haematol*, 2015, 169(6): 834−842.

[7] Yu L, Tu M, Cortes J, et al. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease[J]. *Blood*, 2017, 129(12): 1658−1668.

[8] Zhang L, Zhao AL, Duan MH, et al. Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease[J]. *Blood*, 2019, 133(16): 1720−1728.

[9] Zou WY, Lan HX, Su C, et, al. Retrospective study of Castleman's disease: a report of fourteen cases and review of the literature[J]. *Chin J Clin Oncol* (in Chinese), 2007, 34(22): 195−200.

[10] Murphy C, Hawkes E, Chionh F, et al. Durable remission of both multicentric Castleman's disease and Kaposi's sarcoma with valganciclovir, rituximab, and liposomal doxorubicin in an HHV8-positive, HIV-negative patient[J]. *J Clin Pharm Ther*, 2017, 42(1): 111−114.

[11] Dispenzieri A. Castleman disease[J]. *Cancer Treat Res*, 2008, 142: 293−330.

[12] van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo controlled trial[J]. *Lancet Oncol*, 2014, 15(9): 966−974.

[13] Casper C, Nichols WG, Huang ML, et al. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment[J]. *Blood*, 2004, 103(5): 163−634.

[14] Song Y, Wang J, Wang Y, et al. Requirement for containing etoposide in the initial treatment of lymphoma associated hemophagocytic lymphohistiocytosis[J]. *Cancer Biol Ther*, 2021, 22(10–12): 598−606.

[15] Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease[J]. *Blood*, 2020, 135(16): 1353−1364.

[16] Zhang L, Li Z, Cao X, et al. Clinical spectrum and survival analysis of 145 cases of HIV-negative Castleman's disease: renal function is an important prognostic factor[J]. *Sci Rep*, 2016, 6: 23831.

[17] Joel SP, Shah R, Slevin ML. Etoposide dosage and pharmacodynamics[J]. *Cancer Chemother Pharmacol*, 1994, 34: Suppl: S69−75.

Received 14 December 2022, Revised 5 March 2023, Accepted 30 March 2023