RESEARCH LETTER

Effectiveness of a modified doxorubicin--etoposide-methylprednisolone regimen for the treatment of refractory or relapsed macrophage activation syndrome in adults

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Introduction Hemophagocytic lymphohistiocytosis (HLH) is a group of life-threatening hyperinflammatory diseases triggered by a variety of underlying conditions. When associated with autoimmune diseases, the term macrophage activation syndrome (MAS) is typically used.[1] Glucocorticoid pulse therapy is the prevailing treatment of MAS, but approximately 50% of adult patients are unresponsive.[2] Identification of proper treatment for patients with refractory or relapsed (R/R) MAS remains a challenge. The use of the doxorubicin-etoposide-methylprednisolone (DEP) regimen has shown encouraging results in patients with R/R HLH, but data on R/R MAS are scarce or based only on small cohorts. In the present study, we evaluated the effectiveness and safety of a modified DEP regimen in the largest ever reported cohort of 33 adult patients with MAS.

Patients and methods The inclusion criteria for the study were as follows: 1) meeting the HLH--2004 diagnostic criteria[3]; 2) age over 18 years; 3) diagnosed autoimmune disease; 4) meeting the diagnostic criteria of refractory MAS: treatment with glucocorticoid pulse therapy (methylprednisolone 1 g/day for 3 consecutive days) at least 2 weeks before enrollment without achieving at least a partial response (PR),[4] or meeting at least 3 HLH-2004 diagnostic criteria after achieving a complete response (CR); 5) left ventricular ejection fraction of 50% or greater at the time of enrollment.

Approval was obtained from the Ethics Committee of Beijing Friendship Hospital, Capital Medical University. The requirement for informed consent was waived because of the retrospective design of the study.

All patients underwent gene sequencing and were treated with the modified DEP regimen. The regimen included: liposomal doxorubicin 25 mg/m^2 on day 1; etoposide 100 mg/m^2 on day 1; methylprednisolone 2 mg/m^2 on days 1 to 3, 0.75 mg/m^2 on days 4 to 6, 0.25 mg/m^2 on days 7 to 9, and 0.1 mg/m^2 on days 10 to 21.[5] The clinical effectiveness and side effects were observed. The treatment assessment was carried out every 2 weeks. Details on the evaluation criteria are described in Supplementary material, *Table S1*. The survival time was calculated from the time of MAS diagnosis until death or May 2021.

Statistical analysis Statistical analysis was performed using SPSS 26.0 (IBM Corp, Armonk, New York, United States). Nonnormally distributed variables were reported as medians and ranges. A survival analysis was performed using the Kaplan–Meier method.

Results A total of 33 patients were enrolled, with a median follow-up period of 33 months (range, 1–71 months). Baseline patient characteristics are shown in Supplementary material, *Table S2*. Baseline laboratory values are presented in TABLE 1. Gene sequencing revealed mutations in primary HLH-related genes in 15 patients (45.5%), but no pathogenic mutations were detected. Mutations in the *UNC13D* gene were the most common (5 patients [15.2%]). Details on the genetic variations are shown in Supplementary material, *Table S3*.

After the first course of the modified DEP regimen, 27 patients (81.8%) achieved remission, with a CR rate of 15.5% (5 patients) and a PR rate of 66.7% (22 patients). Six patients (18.2%) showed

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TABLE 1 Baseline laboratory values of the study cohort

Parameter	Cutoff value[a]	Value	Patients with abnormal result, n (%)
NEU, × 10⁹/l	<1.0	4.36 (0.25–27.10)	4 (12.1)
Hgb, g/l	<90	94.00 (57.00–145.00)	22 (66.7)
PLT, × 10⁹/l	<100	98.00 (22.00–471.00)	17 (51.5)
ALT, U/l	>40	56.00 (2.10–924.00)	18 (54.5)
AST, U/l	>35	75.50 (12.00–2057.00)	20 (60.6)
BIL, µmol/l	>17.1	16.42 (4.05–554.80)	16 (48.5)
TG, mmol/l	>3.0	2.89 (0.94–4.39)	16 (48.5)
Fbg, g/l	<1.0	1.96 (0.40–4.73)	10 (30.3)
SF, ng/ml	>500	3785.52 (109.60–100 000.00)	31 (93.9)
sCD25[b], pg/ml	>6400	7515.20 (639.00–31 052.00)	16 (57.1)
NK cell activity[c], %	<15.1	13.60 (3.60–19.12)	14 (73.9)

Data are shown as median (range) unless indicated otherwise.

a According to the HLH-2004 criteria[3]

b Data available in 28 cases

c Data available in 19 cases

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, serum total bilirubin; Fbg, fibrinogen; Hgb, hemoglobin; NEU, neutrophil count; NK, natural killer; PLT, platelet count; sCD25, soluble CD25; SF, serum ferritin; TG, triglycerides

no response, of whom 3 (9.1%) achieved a PR after the second course of the regimen. Three patients (9.1%) died due to MAS progression. During the follow-up period, 6 patients (18.2%) had MAS recurrence and were administered the modified DEP regimen again; all of the 6 patients achieved remission. One of these patients had another MAS recurrence 4 months after completion of the second course of the regimen, and died of MAS before appropriate treatment was initiated. By the end of the follow-up period, 18 patients (54.5%) achieved a CR. Results of the survival analysis are presented in Supplementary material, *Figure S1*.

A total of 107 courses of the modified DEP regimen were received in 39 episodes of MAS. The mean number of courses was 2.7, and the median number of courses was 4 (range, 1–4). Among patients who achieved a CR, the average number of courses was 2.9, and the median number of courses was 4 (range, 1–4).

At the time of enrollment, 22 patients (67.7%) had infections (Supplementary material, *Table S2*). Nine patients (27.3%) developed exacerbated infections, and 2 patients (6.1%) developed new infections. After appropriate antibiotic treatment, the symptoms of infections improved. Twenty-six patients (78.8%) underwent bone marrow biopsy 3 to 4 weeks after the first cycle of the regimen. No evidence of bone marrow suppression was found. Patients with heart disease continued to take appropriate cardiovascular drugs during the treatment. None of the patients developed acute coronary syndrome, malignant arrhythmia, or acute heart failure.

Four patients (12.1%) died as a result of uncontrollable MAS, of whom 3 did not respond to the modified DEP regimen. One patient achieved a PR after treatment with the regimen but died due to HLH recurrence.

Discussion Patients with MAS have a poor prognosis.[6] Early diagnosis and prompt treatment are key to improving the outcomes.[7] Currently, there are no formal guidelines for the management of adult patients with MAS. Based on pediatric experience, glucocorticoid pulse therapy is the mainstay of MAS treatment, but the response rate among adult patients is unsatisfactory.[2] Due to the lack of randomized control studies, management of R/R MAS remains a challenge. In a study by Wang et al,[5] treatment with the DEP regimen showed encouraging results in R/R patients with primary HLH, Epstein-Barr virus–related HLH, and malignancy-related HLH.[5] Unfortunately, data on R/R MAS are lacking in their analysis. In a recent study, effectiveness of the modified DEP regimen in R/R MAS was preliminarily proved. All patients achieved remission after treatment with the DEP regimen combined with ruxolitinib.[8] However, the sample size was very small—only 5 patients were enrolled. In the present study, performed on the largest cohort to date, we demonstrated that the modified DEP regimen was effective and well tolerated by patients with R/R MAS.

In patients with MAS, cytotoxic dysfunction makes it difficult to remove the infected cells or antigen, leading to persistent activation of macrophage and hyperinflammatory conditions. In the modified DEP regimen, doxorubicin is a broad-spectrum chemotherapeutic drug with strong cell toxicity. The distribution of liposomal doxorubicin in inflammatory sites is preferential, while the exposure of normal tissue is limited. Thus, the overactivated macrophages and T cells can be quickly eliminated.[9] Etoposide substantially inhibits the activation of macrophages.[10] It can also reduce the release of proinflammatory molecules by converting lytic to apoptotic cell death.[11] The therapeutic benefits of a high-dose glucocorticoid could be outweighed by the adverse effects in patients who failed to achieve remission after glucocorticoid pulse therapy; therefore, the dose of the glucocorticoid in the regimen was reduced.

Hyperinflammation is responsible for the life-threatening symptoms of MAS; therefore, the immediate aim of the treatment is to suppress hyperinflammation to gain time to treat the underlying diseases.[12] After the first course of the modified DEP regimen, 81.8% of patients achieved remission, with a CR rate of 15.2% and a PR rate of 66.7%. The high response rate to a single course suggests that the immediate aim was achieved rapidly. Additionally, patients' survival could have been prolonged because the underlying disease mainly determines the long-term

prognosis of HLH. Many physicians are concerned that chemotherapy might increase the risk of infection. Nevertheless, it should be emphasized that without proper treatment, persistent agranulocytosis induced by MAS can also lead to severe infections. Our results showed that infections during the treatment with the modified regimen were controllable with appropriate antibiotic treatment. Chemotherapy is not associated with bone marrow suppression. In this study, the results of bone marrow biopsy before and after administration of the DEP regimen were compared and there was no evidence of bone marrow toxicity. We selected liposomal doxorubicin to mitigate the cardiotoxicity. There were no cardiac events directly induced by the modified DEP regimen. Overall, both the rate and the severity of adverse reactions to the modified DEP regimen were acceptable.

Early diagnosis of MAS is essential to improve the prognosis but is hard to achieve. In our study, MAS occurred within 2 months after diagnosis of the autoimmune disease in 54.5% of patients. Thus, for patients with newly diagnosed autoimmune disease, MAS should be considered if there are any suspicious signs. Only 4 patients had a decreased neutrophil count at the time of diagnosis, presumably owing to the autoimmune disease–induced elevation of blood cell counts. A decline in the blood cell counts might provide a clue for early diagnosis of MAS.[13,14] Studies indicate that mutations in the primary HLH-related genes may contribute to the development of MAS.[15] Variants of primary HLH-related genes were observed in nearly half of the patients in this study. Closer monitoring of patients with mutations might be helpful for early identification of MAS. However, gene sequencing is costly and, consequently, it is not available for all patients. Further studies are necessary to develop ways to improve early diagnosis.

In conclusion, treatment of adult R/R MAS remains a serious challenge due to the lack of randomized control studies. However, our study demonstrated that the modified DEP regimen is a promising alternative therapy for adults with R/R MAS owing to the high response rate, rapid action, and satisfactory tolerance.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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