Original Article

Modified SMILE (mSMILE) is active in the treatment of pediatric Epstein-Barr virus-associated natural killer/T-cell lymphoma: a single center experience, case series

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Background: The Epstein-Barr virus-associated natural killer (NK) and T-cell lymphoma (EBV + NK/T cell lymphoma) is a severe illness mainly affecting children and young adults, often resulting in a poor prognosis. To date, there is no consensus on an established treatment strategy. This study aims to evaluate the efficacy and safety of the mSMILE (modified steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy regimen in treating EBV+ NK/T-cell lymphoma and to provide insights into potential treatment outcomes.

Methods: In this study, we conducted a retrospective analysis of the clinical data and treatment outcomes for patients with EBV + NK/T cell lymphoma treated at Children's Hospital of Nanjing Medical University between July 2017 and January 2022. These patients received at least two cycles of the mSMILE chemotherapy, in which a single dose of pegaspargase was substituted for 7 doses of L-asparaginase per cycle.

Results: Eight patients were included in the study: one with extranodal NK/T-cell lymphoma, one with primary nodal NK/T-cell lymphoma, and six with Systemic EBV+ NK/T cell lymphoma of childhood. The results showed that five patients achieved complete remission, two achieved partial remission, and one showed progressive disease, resulting in a complete remission rate of 62.5% and an overall response rate of 87.5%. The 3-year overall survival (OS) and event-free survival (EFS) rates were 87.5% and 75%, respectively. The most common adverse reactions associated with chemotherapy were hematologic toxicities of stages III to IV. Nonhematologic adverse reactions mainly included impaired liver function, infections, and oral mucositis, which were resolved with aggressive anti-infective therapy.

Conclusions: Based on our clinical experience, the mSMILE appears to be a safe and effective treatment option for EBV + NK/T-cell lymphoma, meriting further investigation in late-phase clinical trials.

Keywords: Epstein-Barr virus-associated natural killer and T-cell lymphoma (EBV + NK/T cell lymphoma); chemotherapy; modified steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (mSMILE); hematopoietic stem cell transplantation (HSCT); case series

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Introduction

The Epstein-Barr virus (EBV) has been associated with a wide range of B- and T-cell lymphoproliferative diseases that can affect both immunocompetent and immunocompromised individuals. Among these, EBV-positive natural killer (NK)/T-cell lymphoproliferative disease (T-LPD) is characterized by the proliferation of NK or T cells infected with EBV. The 2017 World Health Organization (WHO) categorization recognizes several distinct disorders with outcomes ranging from benign conditions such as EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) to more protracted illnesses with unpredictable prognoses like chronic active EBV infections (CAEBV) of the T- and NK-cell type, including both cutaneous and systemic forms. This categorization also covers malignant diseases like systemic EBV-positive T-cell lymphoma of childhood, aggressive NK-cell leukemia, extranodal NK/T-cell lymphoma, nasal-type (ENKTL), and primary EBV-positive nodal NK/T-cell lymphoma (1).

EBV-associated NK/T-cell lymphomas are rare malignancies characterized by their aggressive nature and poor prognosis (2-5). While conventional immunosuppressive treatments or CHOP-like regimens are available, the majority of patients experienced tumor recurrence (6). The SMILE (steroid, methotrexate, ifosfamide, l-asparaginase, and etoposide) regimen, a non-anthracycline-based chemotherapy, has been developed for patients with advanced or relapsed/refractory ENKTL (7). Numerous studies have demonstrated the efficacy of L-asparaginase-containing regimens such as SMILE for treating ENKTL (8-10). Recently, Masanori Yoshida *et al.* reported the clinical efficacy of the SMILE regimen in a case of systemic EBV-positive T-cell lymphoma in a pediatric patient (11). In our previous study, we also observed a pediatric patient with primary EBV-positive nodular NK/T cell lymphoma who successfully underwent treatment using a modified SMILE (mSMILE) regimen followed by autologous hematopoietic stem cell transplantation (HSCT) (12). These promising results suggest that the SMILE regimen is a feasible and effective induction therapy for pediatric EBV-associated NK/T-cell lymphoma patients.

Therefore, we have adopted the mSMILE regimen as the primary treatment for pediatric patients with EBV-associated NK/T-cell lymphoma, using at least two cycles of the mSMILE regimen as standard clinical practice. Additionally, to address the high recurrence rate of EBV-associated NK/T-cell lymphoma, patients eligible for HSCT receive consolidation with HSCT.

In this paper, we share our experiences treating consecutive untreated pediatric EBV-positive NK/T-cell lymphoma patients with a mSMILE regimen, in which a single dose of pegylated-L-asparaginase is substituted for six doses of L-asparaginase per cycle. Our initial results in a small cohort of patients were remarkable, suggesting that the mSMILE regimen is effective in these pediatric patients with Systemic EBV positive NK/T-cell lymphoma and deserves further investigation in larger clinical trials. We present this article in accordance with the STROBE and AME Case Series reporting checklists (available at https://tp.amegroups.com/article/view/10.21037/tp-24-90/rc).

Highlight box

Key findings

- Our findings suggest that mSMILE (modified steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) is a safe and effective treatment option for Epstein-Barr virus-associated natural killer (NK) and T-cell lymphoma (EBV + NK/T cell lymphoma).

What is known and what is new?

- EBV + NK/T-cell lymphoma is a severe illness with a poor prognosis, especially in children and young adults.
- Our study validated the efficacy and safety of the mSMILE chemotherapy regimen in this patient population.

What is the implication, and what should change now?

- Our findings suggest that the mSMILE induction chemotherapy followed by initial hematopoietic stem cell transplantation may represent a feasible and effective treatment strategy for patients with EBV-associated NK/T-cell lymphoma, further studies with larger patient cohorts are required.

Methods

Patients

This study was performed in line with the principles of the Declaration of Helsinki (as revised in 2013). The ethics and plan review committee at the Nanjing Medical University approved this study (No. 202305005-1). Written informed consent was obtained from the patients' parents or legal guardians. We obtained diagnostic samples from eight individuals at the onset or upon admission of their treatment. These samples included bone marrow (BM) or lymph node biopsies. We attempted to classify patients based on the 2017 WHO classification and a previously

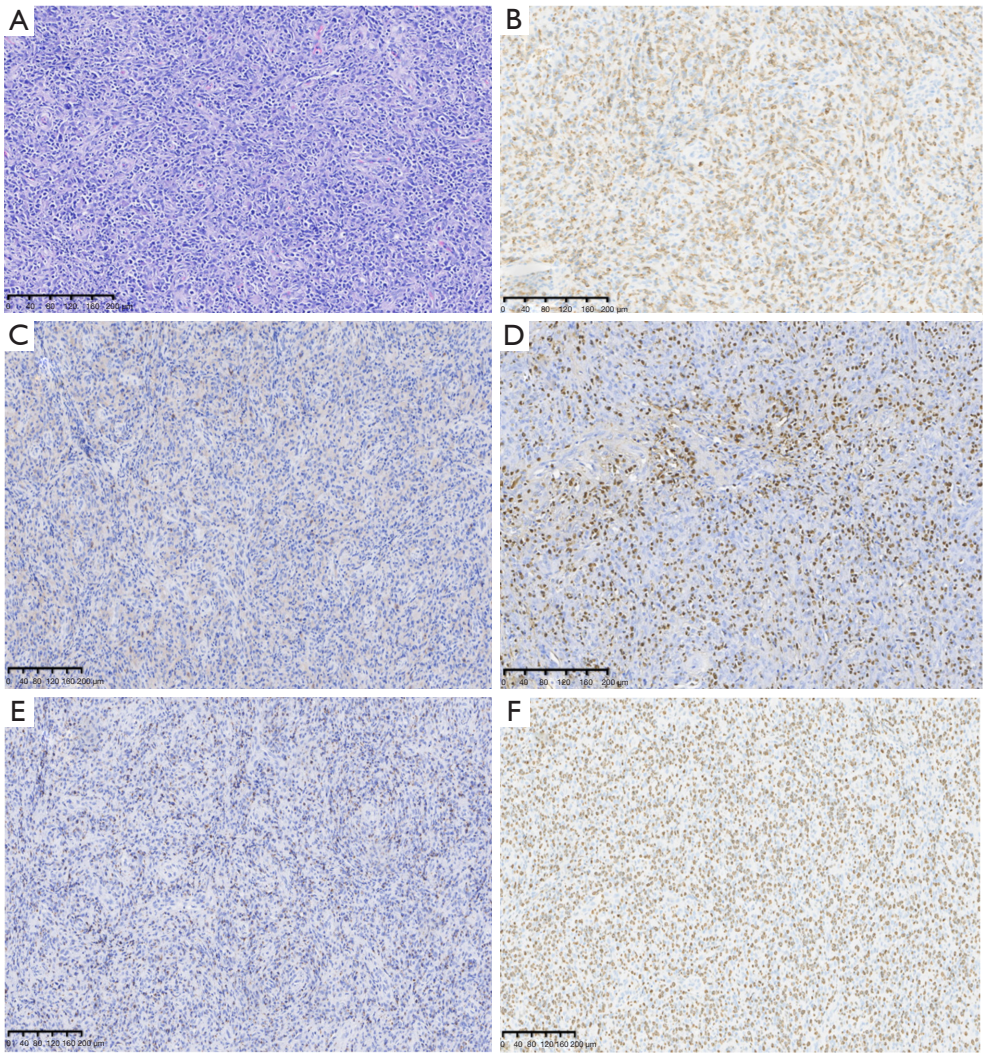

Figure 1 Histologic features of biopsied samples of the lymph node in case 2. The lymphoma cells exhibit a pleomorphic large cell morphology with occasional kidney-like nuclei (A, hematoxylin and eosin stain) and cells' expression of CD3 (B, hematoxylin and eosin stain), CD4 (C, hematoxylin and eosin stain), EBER (D, in situ hybridization), and granzyme B (E, hematoxylin and eosin stain). Approximately 50% of the cancerous cells show nuclear staining for Ki67 (F, hematoxylin and eosin stain). EBER, EBV-encoded RNA; EBV, Epstein-Barr virus.

proposed classification by Kimura *et al.*, which relies on clinical features, laboratory data, disease processes, and pathological/immunotyping and flow cytometry results (2) (*Figures 1*,*2*). Cases with EBV-positive B-cell infiltrates, diffuse large B-cell lymphoma, documented immunodeficiency, EBV-HLH, or familial HLH were excluded from the study. The diagnosis of HLH was determined based on the presence of five or more of the following eight criteria: fever, splenomegaly, cytopenias affecting at least two of three lineages in the peripheral blood, hyperferritinaemia, hypertriglyceridemia and/or hypofibrinogenaemia, haemophagocytosis in BM, spleen or lymph node, low or absent NK-cell activity, and high soluble interleukin-2 receptor levels (CD25). We retrospectively reviewed the records of patients who had previously undergone two or more cycles of the mSMILE regimen at our hospital, with a follow-up date of 1 June 2022. All patients were between the ages of 1 and 16 years and were diagnosed with systemic EBV-positive T-cell lymphoma of childhood, extranodal NK/T-cell lymphoma,

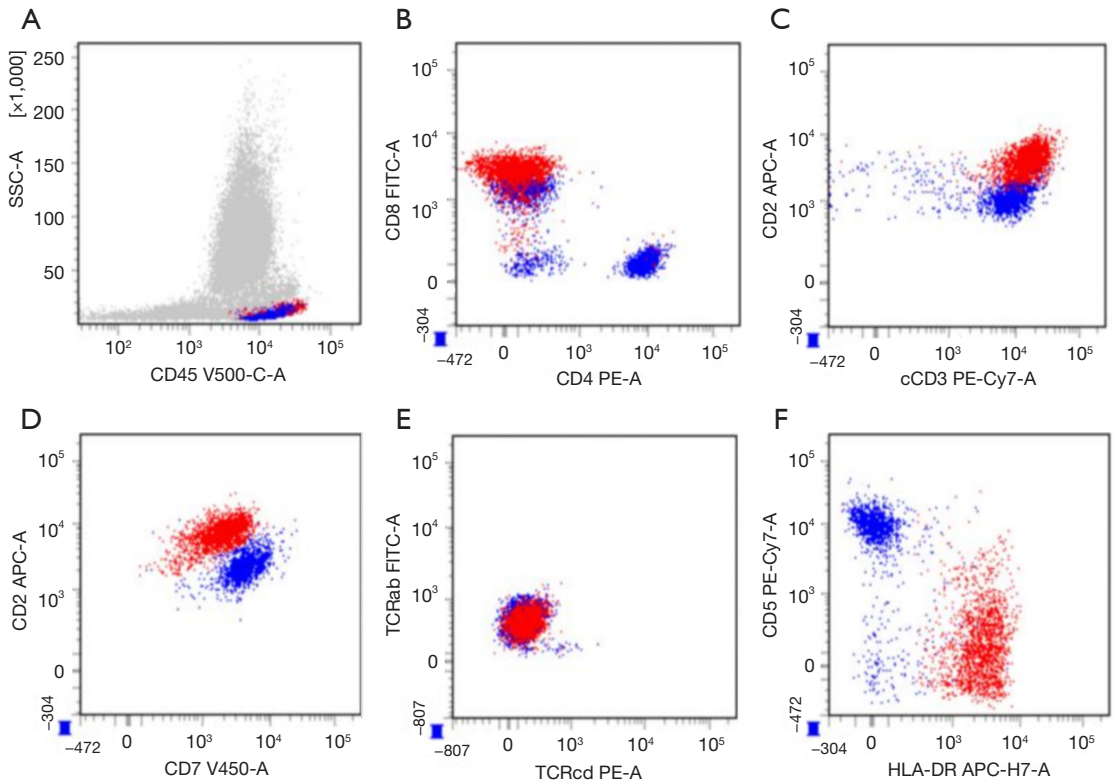

Figure 2 Bone marrow and immunophenotypic findings of S-EBV-TCL with obvious lymphocytic infiltrates (case 1). Corresponding flow cytometry showed atypical $CD8^+$ T cells (7.3%, red color) having bright CD45 and higher side scatter with loss of CD5, slightly dim CD7, and bright CD2/cCD3, TCRαβ and HLA-DR (A-F). The blue dots in the figure represent normal lymphocytes. Gray dots indicate hematopoietic cells other than normal and abnormal T-lymphocytes, such as monocytes, neutrophils, B-lymphocytes, etc. S-EBV-TCL, systemic Epstein-Barr virus-associated T-cell lymphoma; CD, cluster of differentiation; TCR, T-cell receptor; HLA-DR, human leukocyte antigen-DR isotype.

or primary nodal NK/T-cell lymphoma.

Therapy

All patients included in our study who were diagnosed with HLH were initiated on the HLH-94 protocol. Initially, dexamethasone was prescribed at a dosage of 10 mg/m^2 per day. If fever persisted after 3 days, etoposide was introduced at a weekly dosage of 100 mg/m^2. Notably, significant clinical improvement was observed within one to two weeks of commencing the HLH-94 therapy, as evidenced by the resolution of fever, cytopenias, ferritin levels, and sCD25 levels. However, due to the relatively short duration of symptom remission, subsequent chemotherapy with the SMILE regimen was administered during this period. After completing two cycles of mSMILE induction chemotherapy, patients achieving remission proceeded to receive four cycles of consolidation chemotherapy. If remission is not attained following the initial two cycles, patients will be switched to L-DEP or another salvage chemotherapy regimen and subsequently proceeded with allogeneic HSCT (allo-HSCT). Additionally, two patients with extranodal lymphoma underwent autologous stem cell transplantation as a form of consolidation therapy following the completion of six courses of chemotherapy.

The mSMILE chemotherapy protocol consists of 2 g/m^2 intravenous (IV) methotrexate on day 1, followed by 1,500 mg/m^2 ifosfamide and 100 mg/m^2 etoposide on day 1. On days 2–4, patients received 23 mg/m^2 IV dexamethasone and 2,000 U/m^2 IV Pegaspargase on day 8, according to a previously reported protocol. All treatments are administered during hospital days, with granulocyte colony-stimulating factor given during periods of neutropenia to aid recovery.

Table 1 Characteristics of the eight EBV + NK/T-lymphoma patients

Characteristics	Value, n (%)
Sex	
Male	3 (37.5)
Female	5 (62.5)
Histology	
ENKTL	1 (12.5)
NNKTL	1 (12.5)
STCLC	6 (75.0)
Tumor location	
LN	3 (37.5)
BM	3 (37.5)
LN + BM	1 (12.5)
Other	1 (12.5)
Stage	
I/II	1 (12.5)
III	1 (12.5)
IV	6 (75.0)
LDH	
Normal	0 (0.0)
Elevated	8 (100.0)
B symptoms	
Yes	8 (100.0)
No	0 (0.0)
HLH	
Yes	6 (75.0)
No	2 (25.0)

EBV, Epstein-Barr virus; NK, natural killer; ENKTL, extranodal NK/T-cell lymphoma, nasal-type; NNKTL, nodal T/NK-cell lymphoma; STCLC, systemic EBV+ T-cell lymphoma of childhood; LN, lymph node; BM, bone marrow; LDH, lactate dehydrogenase; HLH, hemophagocytic lymphohistiocytosis.

Response and follow-up criteria

To assess the effectiveness of treatments, we utilized the revised criteria established by Cheson for determining treatment responses. A complete response (CR) was defined as the absence of disease and symptoms. A partial response (PR) required a ≥50% reduction in mass size without new lesions. A stable disease applied to patients not meeting CR or PR criteria, and progressive disease involved new lesions or ≥50% increase in lesion size. The overall response rate (ORR) calculated the percentage of CR/PR patients. Progression-free survival (PFS) spanned from treatment initiation to disease progression or death. Overall survival (OS) began on the day of chemotherapy and ended with death or final follow-up.

Adverse event reporting

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was utilized to uniformly describe adverse events experienced by patients, regardless of the assigning of blame.

Statistical analysis

Descriptive statistics were presented as percentages and median values. The length of remission was calculated from the beginning of the treatment to either the first sign of disease progression or the date of the last follow-up, whichever came first. OS was assessed using the Kaplan-Meier method, with the measurement taken from the date of diagnosis to the date of death from any cause, with the date of last follow-up excluded.

Results

Patient characteristics

Table 1 summarizes the patient characteristics, while *Table 2* outlines the histopathologic, immunophenotypic, and other laboratory findings in all patients. Our study involved eight patients who were treated with the mSMILE chemotherapy regimen. This group consisted of one extranodal NK/T-cell lymphoma, one primary nodal NK/T-cell lymphoma, and six cases of systemic EBV + NK/T cell lymphoma in children. Among these patients, three children were male, and five were female, with a median age of 4.5 years. The clinical stages were II-III in 2 cases and IV in 6 cases. The initial symptoms reported by these patients varied and included hemophagocytic syndrome, lymphadenopathy, fever, and nasal congestion. Four cases exhibited BM involvement. All children had elevated lactate dehydrogenase (LDH) values at the onset of the disease (538–2,722 U/L). Plasma EBV-DNA quantification was positive, with a mean value of 2.3E+5 (5.43E+3–5.74E+5). T-cell receptor (TCR) rearrangement was positive in all cases.

Table 2 Biomarkers, EBV-DNA quantification and TCR-rearrangement status of EBV + NK/T-lymphoma patients

Case	Histology	cCD3	CD4	CD8	CD56	TCRb/TCRg	TIA	GranB	Ki-67 (%)	HLA-DR	EBER	TCR-rearrangement	EBV-DNA (copies/mL)
1	STCLC	+	+	+	–	+	N	N	N	+	N	+	1.58E+5
2	STCLC	+	+	–	–	+	+	+	50	N	+	+	2.27E+5
3	STCLC	+	+	+	–	+	+	+	40	N	+	+	2.87E+5
4	STCLC	+	+	+	–	+	N	N	N	+	N	+	5.74E+5
5	STCLC	+	–	+	–	+	+	+	60	N	N	+	2.99E+5
6	STCLC	+	+	+	–	+	–	+	70	N	+	+	5.43E+3
7	ENKTL	+	+	+	+	+	+	+	60	N	+	+	2.65E+5
8	NNKTL	+	–	+	+	–	+	+	80	N	+	+	1.73E+4

EBV, Epstein-Barr virus; TCR, T cell receptor; NK, natural killer; CD, cluster of differentiation; TIA, T-cell intracellular antigen; HLA-DR, human leukocyte antigen-DR isotype; EBER, EBV-encoded RNA; STCLC, systemic EBV+ T-cell lymphoma of childhood; N, not done; +, positive; –, negative; ENKTL, extranodal NK/T-cell lymphoma, nasal-type; NNKTL, nodal T/NK-cell lymphoma.

Table 3 Treatment and outcome of patients

Patient No	Gender	Age (years)	Treatment	Cycle	Outcome	PFS (months)	OS (months)	HSCT
1	F	3	mSMILE L-DEP	2	PR	15	36	Y + allo-HSCT
2	F	4	mSMILE	6	CR	37	37	N
3	M	5	mSMILE	6	CR	36	36	Y + auto-HSCT
4	M	6	mSMILE	6	CR	29	29	N
5	F	2.5	mSMILE	6	CR	19	19	N
6	M	9.5	mSMILE L-DEP	2	PD	4	4	Y + allo-HSCT
7	F	12	mSMILE, P-GEMOX	2	PR	59	59	N
8	F	3	SMILE	6	CR	54	54	Y + auto-HSCT

PFS, progression-free survival; OS, overall survival; HSCT, hematopoietic stem cell transplantation; F, female; mSMILE, modified steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide; L-DEP, pegaspargase + liposomal doxorubicin + etoposide + methylprednisolone; PR, partial remission; Y, received; allo-HSCT, allogeneic HSCT; CR, complete remission; PD, progressive disease; N, not received; M, male; P-GEMOX, pegaspargase + gemcitabine + oxaliplatin.

mSMILE outcome

The mSMILE chemotherapy regimen was administered to eight children, with an average of 4.5 courses each, ranging from two to six cycles. Following chemotherapy, four patients underwent HSCT for consolidation: two underwent autologous HSCT and two received allo-HSCT (*Table 3*). In terms of Efficacy evaluation, 5 cases achieved complete remission (62.5%), 2 cases partial remission (25%), and 1 case progressive disease (12.5%). The complete remission rate was 62.5%, and the ORR was 87.5%. Notably, among the patients who did not achieve complete remission, one patient who exhibited a PR and another patient who did not respond underwent allo-HSCT. Currently, one of these patients remains alive without any signs of relapse, while the other patient succumbed to relapse and passed away. Two other patients received autologous hematopoietic stem cell transplantation after completing six cycles of chemotherapy, and both individuals are currently experiencing disease-free survival. With a median follow-up duration of 36 months, the 3-year OS and PFS rates were 87.5% and 75%, respectively, as illustrated in *Figure 3*.

Side effects of the regimen

Regarding adverse events associated with the mSMILE

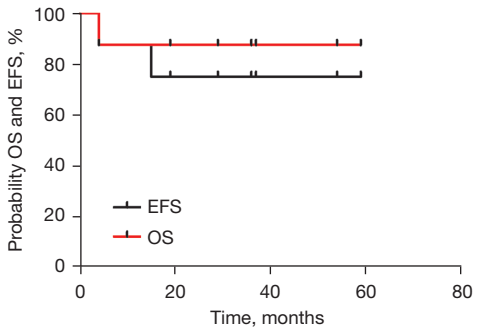

Figure 3 Kaplan-Meier curves plotting the OS/EFS of eight patients with EBV-associated NK/T-cell lymphoma. OS, overall survival; EFS, event-free survival; EBV, Epstein-Barr virus; NK/T-cell, natural killer/T-cell.

regimen, a total of 36 cycles were administered to patients in this cohort study. Cytopenias and elevated transaminase complications were the most common adverse events, followed by infections and oral mucositis. Of particular note, grade 3/4 non-hematologic toxicities, which represent more severe adverse effects, occurred in three patients. These included significant increases alanine aminotransferase and mucositis. Febrile neutropenia was observed in a total of 15 cycles in five patients. No severe bacteremia occurred in any patient.

Discussion

The aim of this study was to investigate the clinical features and treatment outcomes of EBV-associated NK/T-cell lymphoma in children treated with the mSMILE regimen. At diagnosis, these patients exhibited severe clinical characteristics, including advanced-stage disease, elevated LDH levels, B symptoms, and hemophagocytosis, with the disease mainly affecting nodes and BM. The monoclonal nature of all EBV-associated NK/T-cell lymphoma was confirmed through various analysis such as southern blot analysis of EBV-DNA, TCR, or cytogenetic analysis. Despite the small sample size, this cohort provided valuable insights into the safety and efficacy of the mSMILE regimen in children with EBV-associated NK/T-cell lymphomas.

EBV-associated NK/T-cell lymphomas, including systemic EBV-positive T-cell lymphoma of childhood, ENKTL, and primary EBV-positive nodal NK/T-cell lymphoma, are rare entities that predominantly affect Asian children and adolescents. These malignancies are associated with a poor prognosis due to the frequent expression of P-glycoprotein, which extrudes anti-cancer drugs from the cell against a concentration gradient (13). Despite the lack of a consensus treatment strategy, recent reports have highlighted the potential of cytotoxic chemotherapy, autologous BM transplantation, and allo-HSCT in treating this condition (14-16). The SMILE treatment regimen containing l-asparaginase has shown promise in improving the prognosis of advanced ENKTL (8,9,17). Furthermore, recent case reports have described successful treatment of EBV-associated NK/T lymphoma with the SMILE regimen (10,11). Based on the promising results of SMILE treatment in NK cell lymphomas, we attempted to administer chemotherapy using the mSMILE regimen to patients diagnosed with EBV-associated NK/T cell lymphoma at our center.

In our cohort, six out of eight patients presented with hemophagocytic syndrome (HPS) at the initial diagnosis. A previous study has shown that patients who receive etoposide-based chemotherapy regimens (such as the HLH94 or HLH-2004 protocols) have a poor prognosis due to the development of multiple organ failure caused by HPS. Removal of EBV-infected NK/T cells and prevention of macrophage and monocyte activation are crucial in the treatment of HPS (18). Therefore, in this study, our approach aimed at eliminating EBV-infected NK/T cells and preventing further activation of macrophages and monocytes, initially employing the dexamethasone protocol before transitioning to the mSMILE regimen for enhanced effectiveness.

Our single-center experience using the mSMILE regimen in the treatment of pediatric EBV-associated NK/T-cell lymphoma has been promising. Seven out of eight patients who received this treatment have responded, including five achieving a CR. At the time of follow-up, these patients were in disease-free survival. All patients tolerated the chemotherapy well, and no severe adverse events associated with L-asparaginase, such as hemostatic complications, allergies, or pancreatitis, occurred. None died as a result of chemotherapy-related adverse events. However, further research and prospective assessments are required to fully understand the impact of mSMILE treatment on the disease.

The chemotherapeutic response has been improved with L-asparaginase-containing regimens, enabling suitable patients to undergo allogeneic or autologous HSCT as post-remission treatment. Previous reports from Japan indicate a long-term survival rate ranging from 30% to 40%, providing evidence for the value of allo-HSCT (19,20). However,

the relative benefits of reduced-intensity conditioning, traditional myeloablative conditioning, and allogeneic versus autologous HSCT remain controversial (21). In this study, we evaluated three children in complete remission who underwent HSCT (one HLA-haploidentical and two autologous). All of them remained in remission at follow-up, with an average duration of remission reaching 42 months. These patients are still under continuous follow-up observation. Notably, one patient with early BM and abdominal lymph node involvement did not respond well to salvage therapy with the mSMILE and L-DEP regimens. We attempted to perform a forced HSCT for this patient, but he ultimately succumbed to transplant conditioning chemotherapy. This study suggests that HSCT may be an effective means to cure EBV-associated NK/T-cell lymphoma. Future multicenter collaborations are needed to further explore this conclusion. Moreover, to improve HSCT outcomes, timely transplantation and pretransplant remission status are essential.

While our study is limited by its small sample size, short follow-up, and retrospective design, it represents one of the largest series of children with EBV-positive NK/cell lymphoma treated with mSMILE, showing significant clinical efficacy and manageable adverse effects. Furthermore, our data confirm that both autologous and allo-HSCT can improve the prognosis of some EBV-positive NK/cell lymphoma patients. Future studies with larger patient cohorts are essential to confirm these results and identify patients who could benefit most from HSCT, marking an important direction for future research.

Conclusions

In summary, our findings suggest that the mSMILE induction chemotherapy followed by initial HSCT may represent a feasible and effective treatment strategy for patients with EBV-associated NK/T-cell lymphoma, a highly aggressive malignancy. To validate the safety and efficacy of the mSMILE protocol in the treatment of pediatric EBV-positive NK/cell lymphomas, further studies with larger patient cohorts are required. Additionally, exploring the subset of patients who may benefit most from HSCT represents a valuable direction for future research.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE and AME Case Series reporting checklists. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-90/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-90/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-90/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-90/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in line with the principles of the Declaration of Helsinki (as revised in 2013). The ethics and plan review committee at the Nanjing Medical University approved this study (No. 202305005-1). Written informed consent was obtained from the patients' parents or legal guardians.

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