We investigated the effects of L-asparaginase (L-asp) on Epstein-Barr virus (EBV)-positive T/NK lymphoproliferative diseases (EBV-T/NK-LPDs). Seven doses of L-asp (6,000 U/m²) were administered intravenously, with one dose administered on every alternate day. Five consecutive patients were enrolled. Three patients completed the treatment. The clinical symptoms resolved in 1 patient who started the administration 8 months after the onset, being the earliest among the 5 patients. Her EBV-DNA level in whole blood markedly decreased to 0.08 times of that before treatment, and the level in plasma became undetectable. In the other 2 patients whose administration was started 3 and 3.5 years after the onset, however, a remarkable improvement was not detected. Treatment was discontinued in 2 patients because of disease progression or idiopathic dystonia. The mRNA levels of asparagine synthetase in EBV-infected cells were examined. The level from the patient who responded to L-asp treatment was low, but it did not correlate with the effects in the other patients. Liver dysfunction (grades 2 and 3) was observed in 2 patients and neutropenia (grade 3) was noted in 1 patient. In conclusion, the effect of L-asp as monotherapy in EBV-T/NK-LPDs is limited, and early treatment initiation might be effective.

Key words: Epstein-Barr virus-positive T/NK lymphoproliferative disease, peripheral blood EBV-DNA level, L-Asparaginase, asparagine synthetase

Introduction

In the late 70s, some children and young adults suffered from sustained infectious mononucleosis-like symptoms, such as fever, lymphadenopathy and liver damage accompanied by a high anti- Epstein-Barr virus (EBV)-antibody titer in the serum, were reported and named chronic active EBV infection (CAEBV)\(^1\). In the late 80s, it was reported that EBV-infected and clonally proliferating T or NK cells were detected in some CAEBV patients\(^2,3\). The following reports indicated that in CAEBV patients these cells gradually increased in number and became aggressive leading to a disease called extranodal NK/T-cell lymphoma nasal type (ENKL), or aggressive NK-cell leukemia (ANKL)\(^2,4,6\). In addition, 2 unique skin disorders, hypersensitivity to mosquito bites (HMB) and hydroa vacciniforme-like eruption (HV) with infiltration of clonally proliferating EBV-positive T or NK cells also progress gradually and finally develop ENKL or ANKL as well as CAEBV. From these findings, it has been suggested to categorize these diseases as EBV-positive lymphoproliferative
disorders (EBV-T/NK-LPDs). They are now grouped under peripheral T- or NK-cell lymphoma in the WHO classification of lymphoid neoplasms revised in 2008.

The prognosis for EBV-T/NK-LPDs is very poor. According to the report by Kimura and colleagues, 47 patients (44%) died of severe organ complications with median follow-up period of 46 months. One of the reasons is the difficulty for reaching a diagnosis. Morphological changes in the infected cells represent only poor dysplasia, making the diagnosis by pathological examination difficult. Therefore, the diagnosis requires detection of EBV infection on T- or NK-cells and their clonal proliferation. Another reason is that the disease is resistant to chemotherapy. Hematopoietic stem-cell transplantation (HSCT) with reduced intensity conditioning is the only promising treatment strategy for cure, however, HSCT is not feasible for all patients. EBV-T/NK-LPDs patients often experience disease-induced damage in the organs, such as the liver, the heart, and the lungs. Furthermore, the number of elderly patients with EBV-T/NK-LPDs is increasing. Establishing optimal chemotherapy that controls the disease and eradicates EBV-infected cells is crucial.

L-Asparaginase (L-Asp) has been reported to be effective against lymphoid neoplasia such as ENKL, an EBV-positive NK-cell neoplasm as EBV-T/NK-LPDs. Regarding EBV-T/NK-LPDs, the effects of the chemotherapy called Capizzi therapy, which consists of high dose cytarabine followed by L-asp have been reported by Koyama et al. However, it was also reported that cytarabine induced severe adverse events in adult cases of EBV-T/NK-LPDs. According to the previous reports, monotherapy of L-asp induced remission in refractory T-cell lymphoma and ENKL. Furthermore, hematological toxicity of L-asp is not serious in comparison with that of cytarabine. EBV-T/NK-LPDs are classified into peripheral T- or NK-cell lymphoma. In this report, therefore, we prospectively investigated the effects of L-asp on EBV-T/NK-LPDs.

**Materials and Methods**

**Cells and reagents**

The EBV-positive T/NK-cell (EBV-T/NK cell) lines, SNT8, SNT 15, SNT 16, and SNK6 derived from derived EBV-T/NK-LPDs were cultured in RPMI containing 10% human serum and 175 U/ml of human IL-2. IL-2 was purchased from R&D systems (Abington, UK). L-Asp was kindly provided by Kyowa-Hakko Kirin Co., Ltd.

**XTT assay**

XTT assay was performed by the sodium 3V-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)-benzene sulfonic acid hydrate (XTT) colorimetric assay employing the Cell Proliferation Kit II (Roche Molecular Biochemicals according to manufacturer’s instructions.

**Diagnosis of EBV-T/NK-LPDs**

EBV-T/NK-LPDs were diagnosed based on the criteria as suggested by Kimura and colleagues. Briefly, (1) clinical findings described in the previous reports, presence of characteristic clinical findings such as persistent IM-like symptoms, HMB, HV, (2) high EBV load detected in PB by quantitative PCR (> 10^5 copies/μg of EBV-DNA), and (3) EBV infection on T or NK cells. Patients with the following findings were excluded: (1) pathologically defined ENKL, ANKL, or peripheral T-cell lymphoma; (2) HIV positivity. To detect infected cells, we isolated mononuclear cells in PB and divided them into CD19-, CD4-, CD8-, or CD56-positive fractions using antibody-conjugated magnetic beads (IMag Human CD4, 8, and 56 Particles-DM; BD Biosciences, Sparks, MD, USA). EBV-DNA of each fraction was quantified using a real-time quantitative polymerase chain reaction assay. Fractions with identical or higher EBV-DNA titers than that of whole blood (WB) were designated as containing EBV-infected cells. The clonality of EBV-infected cells was determined by Southern blotting using a terminal repeat probe.

**Patients**

Patients diagnosed at Tokyo Medical and Dental University from February 1 to September 14 in 2010 were enrolled in this study. Patients aged ≥14 years and ≤69 years were eligible. Patients whose Eastern Cooperative Oncology Group performance status was 0–2 with sufficient hepatic, renal, cardiac, and pulmonary function were enrolled.

**Treatment Protocol**

The treatment protocol involved 7 administrations of L-asp (6,000 U/m²) every other day. L-Asp was administered intravenously for 2 hours. The primary endpoint was a decrease in plasma EBV-DNA copy number in PB one month after treatment initiation. We defined the reduction rate as a ratio of EBV-DNA copy number in PB of post-treatment to that of pre-treatment. The secondary endpoint was the prevalence of adverse events and improvement of clinical findings.

**Real-time quantitative polymerase chain reaction assay of asparagin synthetase mRNA**

The peripheral blood mononuclear cells (PBMCs) from EBV-T/NK-LPDs patients were isolated by density
gradient centrifugation using Separate-L (Muto Pure Chemical, Tokyo, Japan) and sorted into CD4-, CD8-, or CD56-positive fractions by antibody-conjugated magnetic beads (IMag Human CD19, 4, 8, and 56 Particles-DM; BD Biosciences, Sparks, MD, USA). Total RNA was isolated from them using TRIzol (Life Technologies, Carlsbad, CA, USA). We performed quantification of asparagine synthetase in the RNA of EBV-infected cells by a polymerase chain reaction assay according to the previous report.18

The study complied with the principles of the Declaration of Helsinki and was approved by Internal Review Board on ethical issues of Tokyo Medical and Dental University hospital. It was registered in University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as UMIN000003498. Written informed consent was obtained from all the participants in the study.

Results

In vitro effects of L-asp on EBV-positive T- or NK-cells

In order to confirm the effect of L-asp on EBV-T/NK-LPDs cell lines, we performed XTT assay. Three T-cell lines and one NK-cell line were examined. It showed that L-asp decreased the number of the living cells in all examined EBV-positive cell lines in dose dependent manner (Fig. 1), whereas not in the PBMC from 2 healthy donors. These results indicated that L-asp suppressed the proliferation of both EBV-positive T- and NK-neoplastic cells.

Patients

Five consecutive females (20–62 years; 2 CD4-, 1 CD8-, and 2 CD56-positive cell types of EBV-T/NK-LPDs) were enrolled. Patient characteristics are shown in Table 1.

Two patients (cases 2 and 4) had previously received

<table>
<thead>
<tr>
<th>No</th>
<th>Age/Gender</th>
<th>Cell Type</th>
<th>Monoclonal proliferation</th>
<th>Symptoms at the onset</th>
<th>The duration from the onset to the treatment initiation</th>
<th>Previous treatment</th>
<th>Clinical findings at the treatment initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/F</td>
<td>CD56</td>
<td>(+)</td>
<td>liver dysfunction, pancytopenia myalgia, lymphadenopathy, thrombocytopenia, liver dysfunction</td>
<td>3 Y</td>
<td>(-)</td>
<td>pancytopenia</td>
</tr>
<tr>
<td>2</td>
<td>20/F</td>
<td>CD8</td>
<td>(+)</td>
<td>fever, pulmonary congestion, liver dysfunction</td>
<td>15 M</td>
<td>CsA, Etoposide, PSL</td>
<td>myalgia, infiltration of muscles, elevation of CK and LD</td>
</tr>
<tr>
<td>3</td>
<td>62/F</td>
<td>CD4</td>
<td>(+)</td>
<td>DIC, liver dysfunction fever, hypersensitivity to mosquito bites</td>
<td>8 M</td>
<td>(-)</td>
<td>fever, pulmonary congestion, liver dysfunction</td>
</tr>
<tr>
<td>4</td>
<td>48/F</td>
<td>CD56</td>
<td>(+)</td>
<td>(--)</td>
<td>3.5 Y</td>
<td>CsA, Etoposide, PSL</td>
<td>(--)</td>
</tr>
<tr>
<td>5</td>
<td>26/F</td>
<td>CD4</td>
<td>(+)</td>
<td>fever, nasal erosive lesion</td>
<td>20 Y</td>
<td>(-)</td>
<td>(--)</td>
</tr>
</tbody>
</table>

cyclosporine A (CsA), prednisolone (PSL), and etoposide according to the treatment stated in the previous report. The clinical findings at the initiation of L-asp treatment were as follows: fever in 2 patients (cases 3 and 5) and elevation of the levels of aspartate transaminase (AST) and alanine transaminase (ALT) as well as pulmonary congestion in case 3. Case 2 had systemic muscle pain with elevation of lactate dehydrogenase (LD) and creatine kinase (CK), and accumulation of $^{18}$F-fluorodeoxyglucose (FDG) was detected in the systemic muscles by FDG-positron emission tomography/computed tomography (Fig. 2A). The tissue specimens showed infiltration of EBV-positive cells in the muscles (Fig 2B-D). Although we could not make the diagnosis of lymphoma due to slight atypia of the infiltrating cells, we ascertained that the muscle lesions were due to the disease. The mean load of initial EBV-DNA in WB was $1.2 \times 10^5$ copies/µg DNA (range, $1.2 \times 10^2$–$4.5 \times 10^5$ copies/µg DNA). The load in plasma was $1.1 \times 10^4$–$1.6 \times 10^5$ copies/mL in cases 1, 3, and 5, and negative in cases 2 and 4.

**Clinical course**

The effects and the clinical course are demonstrated in Table 2. The change of EBV-DNA is demonstrated in Fig.3. Cases 1, 3, and 4 completed the treatment. The clinical findings were resolved in case 3. The patient’s EBV-DNA of WB decreased with a reduction rate of
Table 2 The effects of L-Asparaginase

<table>
<thead>
<tr>
<th>No</th>
<th>Age/Gender</th>
<th>Cell type</th>
<th>EBV-DNA in peripheral blood</th>
<th>Reduction rate of EBV-DNA</th>
<th>Effect</th>
<th>AS mRNA</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(copies/μgDNA for WB, copies/mL)</td>
<td>(after T /before T) on symptoms</td>
<td>(AS/GAPDH of the infected cells)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before T (WB)</td>
<td>Before T (plasma)</td>
<td>1M After T (WB)</td>
<td>1M After T (plasma)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23/F</td>
<td>CD56</td>
<td>$6.3 \times 10^4$</td>
<td>$1.6 \times 10^4$</td>
<td>$7.6 \times 10^4$</td>
<td>$8.8 \times 10^4$</td>
<td>1.22</td>
</tr>
<tr>
<td>2</td>
<td>20/F</td>
<td>CD8</td>
<td>$1.2 \times 10^2$</td>
<td>negative</td>
<td>$2.2 \times 10^2$</td>
<td>$1.8 \times 10^2^*$</td>
<td>21.7</td>
</tr>
<tr>
<td>3</td>
<td>62/F</td>
<td>CD4</td>
<td>$1.1 \times 10^1$</td>
<td>$2.2 \times 10^1$</td>
<td>$9.2 \times 10^1$</td>
<td>negative</td>
<td>0.08</td>
</tr>
<tr>
<td>4</td>
<td>48/F</td>
<td>CD56</td>
<td>$4.5 \times 10^2$</td>
<td>negative</td>
<td>$1.2 \times 10^2$</td>
<td>$2.2 \times 10^2$</td>
<td>2.67</td>
</tr>
<tr>
<td>5</td>
<td>26/F</td>
<td>CD4</td>
<td>$6.3 \times 10^1$</td>
<td>$1.1 \times 10^1$</td>
<td>$9.3 \times 10^1$</td>
<td>$8.3 \times 10^1^*$</td>
<td>1.47</td>
</tr>
</tbody>
</table>


Figure 3. EBV-DNA load in the peripheral blood.
A. EBV-DNA load in whole blood before and after treatment (T).
B. EBV-DNA load in plasma before and after treatment (T).
0.08 and that of plasma decreased to an undetectable level. Her treatment was started 8 months after the onset. On the other hand, in cases 1 and 4, whose administrations were started 3 and 3.5 years after the onset, respectively, remarkable improvement in the clinical findings was not detected. Their EBV-DNA in WB and plasma increased after the treatment. In particular, plasma EBV-DNA that had been negative before the treatment turned positive in case 4. Treatment was discontinued in cases 2 and 5. Case 2 suffered dystonia on day 11 and 2 remaining administrations were stopped. She had the infiltration of EBV-positive T-cells in the muscles, as described above. Myalgia and the disease-induced elevation of the levels of CK and LD resolved after the treatment initiation and increased again after the discontinuation of L-asp treatment up to the level of the treatment initiation. However, EBV-DNA in WB increased by 21.7-fold after the treatment initiation. In particular, plasma EBV-DNA, which had been negative before treatment, became detectable after treatment. Case 5 had fever at the initiation of treatment. Despite the treatment, the nasal erosive lesions appeared and showed progression. EBV-DNA levels in WB and the plasma remained almost unchanged. We discontinued the treatment and began immunochemotherapy with CsA, PSL, and etoposide. The fever and the nasal lesions rapidly resolved without a decrease of EBV-DNA levels in the PB. Outcomes were shown in Table 2. Case 3 was stable without any symptoms for 6 months. However, it was observed that EBV-DNA load in the PB increased gradually. Six months after the discontinuation of L-asp, EBV-DNA load of the PB revealed $5.3 \times 10^6$ copies/μgDNA, greater than that at the onset. All patients received allogeneic HSCT. Three patients showed complete remission after HSCT but 2 patients, case 2 and 4, died because of disease progression and septic shock, respectively.

**Adverse events**

Adverse events were summarized in Table 3. Decrease of fibrinogen (grade 2 and 3) and antithrombin III (grade 2) were detected in all patients. Four patients (case 1, 2, 3, and 4) required the administration of fresh frozen plasma. All patients required the supplementation of antithrombin III. Grade 3 neutropenia was detected in case 3. Additional adverse events were also shown in Table 3: liver dysfunction (grade 2 and 3 in cases 2 and 4, respectively) and neutropenia (grade 3 in case 3). Case 2 suffered dystonia as described above. We performed magnetic resonance imaging of the brain and a lumbar puncture in this patient. No lesion was present in the central nervous system that could have caused this attack. Since this patient had been diagnosed with dystonia before the onset of EBV-T/NK-LPDs, the attack was considered not to be directly attributable to L-asp treatment. Acute pancreatitis and allergic reaction were not detected.

**Expression of asparagine synthetase**

<table>
<thead>
<tr>
<th>No</th>
<th>Age/Gender</th>
<th>Cell Type</th>
<th>Adverse events (≥ Grade 2)</th>
<th>Treatment completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/F</td>
<td>CD56</td>
<td>decrease of fibrinogen (Grade 3)</td>
<td>completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of antithrombin III (Grade 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of fibrinogen (Grade 2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20/F</td>
<td>CD8</td>
<td>decrease of fibrinogen (Grade 2)</td>
<td>discontinued due to dystonic attack</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of antithrombin III (Grade 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dystonic attack (Grade 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>liver dysfunction (Grade 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of fibrinogen (Grade 3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>62/F</td>
<td>CD4</td>
<td>decrease of antithrombin III (Grade 2)</td>
<td>completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>neutropenia (Grade 3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>48/F</td>
<td>CD56</td>
<td>decrease of fibrinogen (Grade 3)</td>
<td>completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of antithrombin III (Grade 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>liver dysfunction (Grade 3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26/F</td>
<td>CD4</td>
<td>decrease of fibrinogen (Grade 3)</td>
<td>discontinued due to progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease of antithrombin III (Grade 2)</td>
<td></td>
</tr>
</tbody>
</table>

NC: no change, PD: progressive disease; F: female,
We examined asparagine synthetase mRNA levels in EBV-infected cells from EBV-T/NK-LPDs patients. The EBV-positive cells were isolated and obtained for AS mRNA detection by RT-PCR as described in ‘Materials and Methods’ section. mRNA levels in case 3, which responded to L-asp, were relatively low (Table 2). However, mRNA level in case 5, which showed disease progression, also was low.

**Discussion**

Although our in vitro assay and the previous reports suggested that L-asp might have effects on EBV-T/NK-LPDs, it elicited effects on symptoms in only 1 of the 5 patients with EBV-T/NK-LPDs in the present study. L-Asp decomposes asparagine, which is indispensable for human cell survival, and induces asparagine deficiency, resulting in apoptosis of tumor cells. Since fibrinogen and antithrombin III were markedly decreased in all patients, asparagine was considered to be exhausted sufficiently in them. Previous reports indicated that the effects of L-asp were dependent upon the level of asparagine synthetase expression in tumor cells: Ando et al. investigated asparagine synthetase expression in NK-cell tumors and demonstrated that the effects were related to the expression level in ENKL. Asparagine synthetase expression in EBV-infected cells of EBV-T/NK-LPDs, such as CAEBV, HMB, and HV has not been reported. In the present study, patients who responded to the treatment had relatively low expression of asparagine synthetase. However, expression was lower in case 5, who did not respond to treatment, than that in case 3. Despite the small study cohort, these results suggested that the level of asparagine synthetase was not sufficient to determine the effect of L-asp on EBV-T/NK-LPDs.

Although the viral load was not reduced, the clinical symptoms were resolved after the administration in case 2. The duration from the onset to the treatment initiation was relatively short.15 months and 8 months in the responders for L-asparaginase, case 2 and case 3, respectively. On the other hand, the duration of other patients without response was 3 to 20 years (mean 8.8 years). The results indicated that early treatment initiation might be associated with the effects. Kimura and colleagues reported that patients whose time from onset to HSCT was less than 30 months had significantly higher overall and event-free survival rates in patients with T-cell infection. Clonal evolution of the EBV-infected cells during the course may cause the resistance for the chemotherapy. In order to clarify which factor is responsible for these effects, a study involving a much larger cohort is necessary to be conducted.

We examined EBV-DNA levels in PB during treatment. In ENKL, another EBV-positive NK cell tumor, EBV-DNA load in plasma reflect the amount of tumor as well as its prognosis. However, the correlation between EBV-DNA levels in PB and EBV-T/NK-LPDs status is controversial. Kimura et al. reported that the level in PB mononuclear cells decreased significantly after transplantation and suggests that EBV-DNA can be a marker for EBV-T/NK-LPDs. In the present study, the results were complicated to be interpreted. In case 3, improvement of the symptoms was shown with a decrease in EBV-DNA load in WB as well as in plasma, and the load especially in plasma, reflected disease status. Conversely, in case 2, in which a clinical response to L-asp was observed, EBV-DNA levels in WB and plasma did not parallel with disease status. Recently we also reported that EBV-DNA in PB of EBV-T/NK-LPDs did not correlate with disease sensitivity. More cases should be studied to determine whether EBV-DNA load can be used as a molecular marker of EBV-T/NK-LPDs.

Several adverse events were observed in the present study. Elevation of the levels of AST and ALT was observed in 2 patients (40%), case 2 and case 4. L-Asp hydrolyzes L-asparagine, which results in suppressed protein synthesis and the death of lymphoid tumor cells in which the synthesis of L-asparagine was suppressed. Hepatic toxicity with L-asp is probably due to suppression of protein synthesis. The liver is a target of L-asp and cytarabine, was reported by Koyama et al. to have an effect on 2 EBV-T/NK-LPDs children. However, severe adverse events mainly due to cytarabine have also been reported. In our hospital, 3 adult patients were treated with Capizzi therapy, and all of them developed grade 4 fever and/or pulmonary congestion during administration of cytarabine without eradication of EBV-infected cells. Ek et al. reported upon the administration of 2 g/m² cytarabine every 12 h to 16 children with leukemia and lymphoma, and 13 patients developed a temperature of >38°C. They also reported that levels of inflammatory cytokines such as
tumor necrosis factor-α, interleukin-6, and interferon-γ were elevated in the patients. These cytokines can be produced and secreted by EBV-infected T-cells. Actually the levels of them are significantly elevated in EBV-T/NK-LPDs, indicating that severe acute-onset reactions after cytarabine administration may be peculiar to EBV-T/NK-LPDs patients. We could not determine the effect of L-asparaginase on EBV-T/NK-LPDs. The indication for Capizzi therapy for EBV-T/NK-LPDs needs to be carefully decided.

In conclusion, the effect of L-asparaginase as monotherapy in EBV-T/NK-LPDs was limited, however, early treatment initiation might be effective. Further study is necessary to establish treatment strategy as EBV-T/NK-LPDs have diverse clinical features according to clinical stage.

Acknowledgments

We thank Ms. Kaori Okada for excellent technical assistance. This work was supported by a grant from the Ministry of Health, Labour and Welfare of Japan (grant number, H24-Nanchi-046) as well as a grant from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (23591375).

Disclosure

The authors declare no conflicts of interest.

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