**Predictive Biomarkers and Personalized Medicine**

**Pretreatment EBV-DNA Copy Number Is Predictive of Response and Toxicities to SMILEChemotherapy for Extranodal NK/T-cell Lymphoma, Nasal Type**


**Abstract**

**Purpose:** Extranodal NK/T-cell lymphoma, nasal type (ENKL) is an Epstein–Barr virus (EBV)–associated lymphoma for which a new chemotherapeutic regimen called SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) recently showed promising results.

**Experimental Design:** The amount of EBV-DNA was prospectively measured in whole-blood and plasma samples by real-time quantitative PCR from 26 patients registered in the SMILE phase II study.

**Results:** Before treatment, the EBV-DNA was detected in 22 samples of whole blood with a median number of 3,691 copies/mL (range: 0–1.14 × 10^7), but 15 samples of plasma with a median of 867 copies/mL (range: 0–1.27 × 10^7). Results of these 2 measurements of EBV-DNA well correlated (R^2 = 0.994, P < 0.001). The overall response rate to SMILE was significantly higher in patients with less than 10^5 copies/mL of EBV-DNA in whole blood at enrollment (90% vs. 20%, P = 0.007) and in patients with less than 10^4 copies/mL of EBV-DNA in plasma (95% vs. 29%, P = 0.002). The incidence of grade 4 toxicity of SMILE other than leukopenia/neutropenia was significantly higher in patients with 10^5 copies/mL of EBV-DNA or more in whole blood (100% vs. 29%, P = 0.007) than that of others and in patients with 10^4 copies/mL or more in plasma (86% vs. 26%, P = 0.002).

**Conclusions:** These findings suggest that whole blood is more sensitive for clinical use than plasma. The EBV-DNA amount in whole blood was useful for predicting tumor response, toxicity, and prognosis after SMILE chemotherapy for ENKL. *Clin Cancer Res; 18(15); 4183–90. ©2012 AACR.*

**Introduction**

Epstein–Barr virus (EBV) causes a variety of benign and neoplastic diseases, including infectious mononucleosis, posttransplantation lymphoproliferative disorder (PTLD) and EBV-associated malignancies such as lymphomas, including extranodal NK/T-cell lymphoma, nasal type (ENKL), Hodgkin lymphoma, Burkitt lymphoma, age-associated large B-cell lymphoma, and several other T-cell lymphomas (1–3). ENKL is a rare subtype of non-Hodgkin lymphoma, mainly occurs in the nasal/paranasal area, skin, or gastrointestinal tract and is much more common in Asia and Latin America than in Western countries (4–6). The prognosis of ENKL was poor under conventional chemoradiotherapy and/or chemotherapy (4, 7) but has recently improved by concurrent chemoradiotherapy (8, 9) or newly developed SMILE chemotherapy, comprising the steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (10, 11).

This type of lymphoma is invariably associated with episomal infection of EBV in the tumor cells, which implies its tumorigenic role. The presence of EBV-DNA in peripheral blood has been used as a surrogate marker for estimating tumor amount in several EBV-associated malignancies.
Peripheral blood of patients with extranodal NK-cell lymphoma, nasal type (ENKL) contains fragmented Epstein–Barr virus (EBV)-DNA. The amount of EBV-DNA can be a good marker for estimating the tumor burden and prognosis of ENKL patients. We recently developed a novel chemotherapeutic regimen, SMILE, comprising steroid, methotrexate, ifosfamide, l-asparaginase, and etoposide. The tumor response rate and survival rate was dramatically improved. However, it is known that the prognostic significance of certain factors may vary when the treatment modality changes. Therefore, the significance of EBV-DNA was analyzed in this study. Consequently, pretreatment whole blood and plasma EBV-DNA were predictive of response and prognosis. Multivariate analysis showed that plasma EBV-DNA was a significant prognostic factor. Furthermore, the EBV-DNA load was also predictive of adverse events by chemotherapy. Prediction of toxicity is particularly important for the SMILE regimen because it is excessively toxic for some patients.

Translational Relevance
Peripheral blood of patients with extranodal NK-cell lymphoma, nasal type (ENKL) contains fragmented Epstein–Barr virus (EBV)-DNA. The amount of EBV-DNA can be a good marker for estimating the tumor burden and prognosis of ENKL patients. We recently developed a novel chemotherapeutic regimen, SMILE, comprising steroid, methotrexate, ifosfamide, l-asparaginase, and etoposide. The tumor response rate and survival rate was dramatically improved. However, it is known that the prognostic significance of certain factors may vary when the treatment modality changes. Therefore, the significance of EBV-DNA was analyzed in this study. Consequently, pretreatment whole blood and plasma EBV-DNA were predictive of response and prognosis. Multivariate analysis showed that plasma EBV-DNA was a significant prognostic factor. Furthermore, the EBV-DNA load was also predictive of adverse events by chemotherapy. Prediction of toxicity is particularly important for the SMILE regimen because it is excessively toxic for some patients.

(12–14). In particular, after organ transplantation, increasing loads of EBV in whole blood, lymphocytes, and plasma are associated with corresponding increases in the risk of PTLD (14). For nasopharyngeal carcinoma, plasma EBV-DNA load is known to be useful for monitoring disease activity and predicting the outcome of treatment (15, 16). The disease activity and prognosis of ENKL can also be monitored by measuring circulating EBV-DNA in plasma (17). For patients registered to the SMILE phase II study, we simultaneously conducted a prospective observational study, SMILE-EBV study, in which the amounts of EBV-DNA in whole blood and plasma were evaluated for ENKL.

Materials and Methods

Study design
The aim of this study is to evaluate the copy numbers of EBV-DNA from whole blood and plasma in patients with ENKL who received SMILE chemotherapy. The predictive value of EBV-DNA for tumor response, toxicity, and prognosis was analyzed, as well as the preference of samples from whole blood or plasma. The eligibility criteria, treatment, and response were described in the report of the phase II study (11). EBV-encoded small RNA (EBER) in situ hybridization positivity was counted in accordance with our previous study (18). A total of 38 patients were enrolled: 26 from Japan, 6 from Hong Kong, and 6 from South Korea. The amounts of EBV-DNA were measured in whole-blood and plasma samples from patients participating in this phase II study at 3 time points: before the treatment, after 2 courses of SMILE and after a series of treatments. Because of the lack of an international standardized method for quantification of EBV-DNA, the 26 patients from Japan were the subjects for this study. All samples were measured in a central laboratory. Registration onto the study was conducted by facsimile from the participating institutes to the C-SHOT Data Center (Nagoya, Japan), simultaneously with the entry into the SMILE study. The study was approved by both the Protocol Review Committee and the Institutional Review Board of each institution in Japan. Written informed consent was obtained from all of the patients. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR number, UMIN000000741), as an associated but separate study of SMILE phase II (UMIN-CTR number, UMIN000000712).

Response and toxicity criteria
Complete response was defined as the complete disappearance of all objective signs of disease, including enlarged lymph nodes or hepatosplenomegaly at restaging. Partial response was defined as at least a 50% reduction of tumor volume without the occurrence of new lesions at restaging. Progressive disease was defined as a greater than 25% increase in the sum of tumor lesions or the emergence of one or more new lesions or clinical symptoms that indicate disease progression. No response was defined as any response that did not fall into the categories defined above. If a patient died of any cause before day 42 of the second course of SMILE and could not undergo the defined restaging procedure, the patient’s response was recorded as early death. The overall response rate (ORR) was defined as the proportion of all patients who could be evaluated for response who experienced complete or partial response. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0.

Quantification of EBV-DNA
A 5-mL patient peripheral blood was obtained, sent to the central laboratory (Nagoya University Graduate School of Medicine), and divided into whole-blood and plasma samples. DNA was extracted from 200 μL of either whole blood or plasma, using QIAamp DNA blood kits (Qiagen K.K.). A real-time quantitative PCR assay was carried out and the result was expressed as copies per 1 mL of sample, as previously described (19, 20). The minimum detection level was 2 copies per reaction that was equivalent to 100 copies/mL for whole blood or plasma.

Statistical analysis
Regression analysis compared the copy numbers in whole blood and plasma. Fisher exact test was used to compare the responses or toxicities to the SMILE chemotherapy. Mann–Whitney U test and Kruskal–Wallis test were used to compare the levels of EBV-DNA between patient groups. Cut-off value of the categorization by EBV-DNA levels were determined by the receiver operating characteristic analysis. Patient survival data were analyzed by the method of Kaplan and Meier and were compared by log-rank test. Univariate and multivariate analyses were carried out using Cox proportional hazard model. Data were analyzed with STATA version 11 and SPSS (SPSS) software.
Results

Patient characteristics

The baseline characteristics of 26 eligible patients are listed in Table 1. The median age was 46.5 (range: 17–67) years, and the male:female ratio was 14:12. Twelve patients (46%) had newly diagnosed stage IV disease, 11 were in first relapse, and 3 were in the primary refractory status. EBER in situ hybridization was positive in all specimens, with a median positivity of 68% (range: 12%–96%) of lymphoma cells.

Amount of EBV-DNA and correlation between whole blood and plasma

EBV-DNA was detected in 22 samples of whole blood (median: $3.7 \times 10^7$, range: $0–1.1 \times 10^7$ copies/mL) and 15 samples of plasma (median: $8.7 \times 10^5$, range: $0–1.3 \times 10^7$ copies/mL). The level of EBV-DNA was not different among the 3 disease state (newly diagnosed, relapsed or refractory) groups at enrollment both in whole blood ($P = 0.19$ by Kruskal–Wallis test) and in whole blood ($P = 0.22$). An inconsistent result was seen in 9 patients. EBV-DNA was positive in whole blood but was negative in plasma in 8 patients. Conversely, in another patient, the EBV-DNA was only detected in plasma. EBV-DNA was not detected in either whole blood or plasma in 3 patients (nos. 9, 23, and 25). The concordance rate between whole blood and plasma was 65% (17 of 26). The viral DNA copy numbers were compared between whole blood and plasma before SMILE chemotherapy. A strong correlation was found between the amounts in whole blood and those in plasma ($r = 0.997, P < 0.001$, Fig. 1). No differences were found for the EBV-DNA level among patients with newly diagnosed stage IV, relapsed and refractory status ($P = 0.19$ for whole blood and $P = 0.24$ for plasma). No significant correlation was found between EBER positivity and plasma or whole blood EBV-DNA level (Supplementary Fig. S1).

Dynamic changes of EBV loads in whole blood and plasma before and after treatment

EBV loads in whole blood or plasma from the 16 patients (8 with complete response, 7 with partial response, and 1 with progressive disease) were measured before the treatment, after 2 courses of SMILE chemotherapy, and after a series of treatments. Viral load declined in most patients with complete response or partial response after 2 courses of SMILE chemotherapy and/or after a series of treatments. Viral load declined in most patients with complete response or partial response after 2 courses of SMILE chemotherapy and/or after a series of treatments (Fig. 2). However, 5 patients with complete or partial response did not show the decrease of viral load. Of these, 2 patients experienced disease recurrence, and another patient died of transplant-related mortality in complete response. Other 2 patients maintained response at the time of last follow-up.

Correlation of the amount of EBV-DNA in blood samples and response or toxicities to the therapy

Among the 26 patients, there were 12 patients with complete response, 8 with partial response, 1 with no response, 3 with progressive disease, and 2 with early death (Table 2), and the ORR was 77%. For patients with less than
10^5 copies/mL of EBV-DNA in whole blood, the ORR was 90% (19 of 21), but was 20% (1 of 5) in patients with 10^5 copies/mL or more \((P = 0.005)\). In addition, the ORR was 95% (18 of 19) in patients with less than 10^4 copies/mL of EBV-DNA in plasma, but was 29% (2 of 7) in patients with 10^5 copies/mL or more \((P = 0.002)\). All 3 patients without detectable EBV-DNA in either whole blood or plasma attained complete response. The amounts of EBV-DNA before treatment were not significantly different between patients with complete response and those with partial response (whole blood, \(P = 0.82\); plasma, \(P = 0.68\)).

Grade 4 leukopenia (77%) and neutropenia (88%) were commonly observed. Grade 4 anemia was encountered in one patient and thrombocytopenia was seen in 9 patients. The nonhematologic grade 4 toxicities included infection \((n = 2)\), alanine aminotransferase elevation \((n = 1)\), and encephalopathy \((n = 1)\); 3 patients experienced grade 4 somnolence, which was complicated by a grade 3 infection in one patient and by grade 4 encephalopathy in another patient. One patient experienced grade 2 pancreatitis and had complications from grade 4 hyponatremia, hyperamylasemia, and appetite loss. Grade 4 toxicity other than leukopenia/neutropenia was significantly higher in patients with 10^5 copies/mL of EBV-DNA or more in whole blood \((100\% \text{ vs. } 29\%, P = 0.007)\). Grade 4 toxicity other than leukopenia/neutropenia was also significantly higher in patients with 10^4 copies/mL of EBV-DNA or more in plasma \((86\% \text{ vs. } 26\%, P = 0.002; \text{Table 2})\).

**Prognostic significance of EBV-DNA**

Patients with 10^5 copies/mL of EBV-DNA or more in whole blood showed significantly lower survival than those with less than 10^5 copies/mL \((P < 0.0001)\). Similarly, the prognosis of patients with 10^4 copies/mL of EBV-DNA or more in plasma was significantly worse than that in those with less than 10^4 copies/mL \((P < 0.0001)\). EBER positivity of more than 75% was also a factor.

**Figure 2.** Serial analysis of EBV loads in blood samples from the patients with ENKL. The EBV-DNA concentrations in whole blood or in plasma from the patients were measured using real-time PCR assay before SMILE chemotherapy, after 2 courses of SMILE chemotherapy and after a series of treatments. A, viral loads in whole blood in patients with complete response. B, viral loads in plasma in patients with complete response. C, viral loads in whole blood in patients with partial response. D, viral loads in plasma in patients with partial response. Dotted lines show the detection limits indicating 100 copies/mL of plasma or whole blood. CR, complete response; PR, partial response.

**Table 2.** Correlation of the levels of EBV-DNA and response/adverse events to SMILE chemotherapy for newly diagnosed stage IV, relapsed or refractory ENKL

<table>
<thead>
<tr>
<th>Whole blood EBV-DNA</th>
<th>Plasma EBV-DNA (copies/mL)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(\geq 10^5) copies/mL</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
</tr>
<tr>
<td>ED</td>
<td>2</td>
</tr>
<tr>
<td><strong>Adverse event</strong></td>
<td></td>
</tr>
<tr>
<td>Any grade 4a</td>
<td>5</td>
</tr>
<tr>
<td>No grade 4</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; ED, early death; PD, progressive disease; PR, partial response; NR, No response.

aGrade 4 adverse events other than leukopenia and neutropenia.
associated with poor prognosis (Fig. 3C). Plasma and whole blood EBV-DNA before SMILE chemotherapy were significant prognostic factors for overall survival by univariate analysis, as well as serum lactate dehydrogenase (LDH) elevation, B symptom, and EBER positivity (Table 3). Multivariate analysis showed that LDH elevation [HR, 8.5; 95% confidence interval (CI), 1.9–38.0] and pretreatment whole blood EBV-DNA [HR, 65.5; 95% CI, 5.3–813.7] were significant prognostic factors. Plasma EBV-DNA was not prognostic (HR, 3.90; 95% CI, 0.70–21.8) if adjusted by LDH elevation using multivariate analysis. EBER positivity showed marginal significance (HR, 3.3; 95% CI, 0.95–11.8) if included in the model with LDH elevation.

Discussion

For EBV-associated malignancies, the significance placed on EBV-DNA in peripheral blood as a biomarker has increased in recent decades. Previous studies have reported that the level of EBV-DNA in a peripheral blood compartment is a useful biomarker in EBV-associated malignancies (14, 21). Lei and colleagues found a significant reduction of plasma EBV-DNA in patients with EBV-associated lymphoid malignancies (Hodgkin lymphoma, nasal NK/T cell lymphoma, PTLD, and Burkitt lymphoma) during the course of effective therapy (21). In addition, disease progression was associated with a rapid increase in plasma EBV-DNA levels in patients with ineffective therapy. Gandhi and colleagues showed that EBV-DNA is specifically detected in plasma of EBV-positive Hodgkin lymphoma patients before treatment (22). Viral DNA was undetectable following therapy in responsive patients and patients with long-term remission. Patients who experienced relapse had a significantly higher plasma EBV-DNA concentration before treatment. The plasma DNA concentration was persistently low or undetectable in patients with complete clinical remission. Overall survival and relapse-free survival were significantly higher for patients with a pretreatment plasma EBV-DNA level of less than 1,500 copies/mL. Au and colleagues reported that plasma EBV-DNA level is valuable as a tumor biomarker and for prognostication in EBV-positive lymphoma (17). EBV-DNA in plasma became undetectable for patients in remission but was elevated for those with refractory disease. A high level of EBV-DNA was significantly associated with inferior overall survival by multivariate analysis. Subgroup analysis of NK cell lymphoma showed that the level of EBV-DNA was also correlated with disease stage. Presentation of a high level of EBV-DNA was also significantly associated with inferior overall survival by multivariate analysis in their cohort. Prognostic factors of lymphoma may change when the treatment modality changes (23). In this study, however, EBV-DNA copy number in plasma or whole blood was also predictive of response and survival of ENKL patients who received SMILE chemotherapy, in agreement with other observations in the literature.

Another novel finding is that severe adverse events of the chemotherapy were also predictable using the EBV-DNA amount, which has not been identified by other studies in the literature. This analysis is only possible by examining patients who receive exactly the same treatment, ideally subjects of prospective studies. Because the level of EBV-DNA was not different by the 3 disease status groups (newly diagnosed, relapsed, or refractory), we examined the patients together in this study. As an interpretation of this finding, patients with higher tumor burden may experience more severe toxicity because of poor general condition or tissue damage by the tumor. Another hypothesis is that the
Correlation was detected between the viral copy numbers in whole blood and those in plasma. EBV-DNA was more frequently detected in whole-blood samples before treatment. Notably, EBV-DNA was only detected in whole blood in 8 patients, whereas it was only positive in plasma in one patient. This suggests that whole blood is more suitable than plasma to examine the EBV-DNA for ENKL. The reason for the phenomenon that EBV-DNA was only detected in whole blood remains undetermined. Among such 8 patients in this study, only 4 patients showed bone marrow involvement, and none accompanied leukemic presentation. The only possible explanation is that EBV-DNA might be lost or degraded in the fractionation procedure. Another point of interest is that EBV-DNA was not detected in either whole blood or plasma in 3 patients, although EBER was positive in tissue samples. Therefore, EBV-DNA detection in peripheral blood cannot be used as an alternative to the histologic detection of EBV or the diagnosis of ENKL. Moreover, the levels of $10^5$ copies/mL of EBV-DNA in whole blood and $10^4$ copies/mL of EBV-DNA in plasma seem to be cut-off values: the patients with copy numbers lower than these showed significantly better outcome. These 2 copy numbers also showed clinical value to predict severe adverse events.

In conclusion, our study indicates that the level of EBV-DNA in plasma or whole blood can predict response and adverse events of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory ENKL. Whole-blood samples were more suitable for this purpose, although plasma was preferable for other purposes such as diagnosis of EBV infection.

disclosure of potential conflicts of interest
R. Suzuki received honoraria from Kyowa-Hakko Kirin Company. K. Oshimi is currently an employee of Eisai Pharmaceutical Co., Ltd. (Tokyo, Japan). No potential conflicts of interest were disclosed by the other authors.

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Table 3. Prognostic factors affecting overall survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unfavorable factors</th>
<th>Hazard ratio (CI)</th>
<th>P</th>
<th>Hazard ratio (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;50 years</td>
<td>0.5 (0.2–1.9)</td>
<td>0.33</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LDH level</td>
<td>Elevated</td>
<td>8.6 (2.4–30.4)</td>
<td>0.001</td>
<td>8.5 (1.9–38.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>B symptom</td>
<td>Present</td>
<td>5.0 (1.3–19.0)</td>
<td>0.02</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WB EBV-DNA</td>
<td>≥10^6 copies/mL</td>
<td>53.2 (5.9–482.0)</td>
<td>&lt;0.001</td>
<td>66.5 (5.3–813.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma EBV-DNA</td>
<td>≥10^6 copies/mL</td>
<td>10.3 (2.9–36.3)</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>EBER</td>
<td>&gt;75%</td>
<td>4.0 (1.2–13.7)</td>
<td>0.03</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Final model.
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Acknowledgments
The authors thank staff at all participating institutions in this study: Tokyo Medical and Dental University, Kanagawa Cancer Center, Yokohama City University. Otsuka Kosei Hospital, Saga University, Yamanashi University, Shinsu University, NTT Medical Center Tokyo, Fukushima Prefectural Medical College, Kurashiki Central Hospital, Niigata University, Kyoto Medical Center, Nagano Red Cross Hospital, Tsukuba University, and Juntendo University.

The authors also thank the members of Central Pathology Review Board (Drs. Koichi Oshihama at Kumene University and Kengo Takashiki at Cancer Institute), Central Imaging Review Board (Drs. Takao Kodama and Takanori Yano at Miyazaki University, and Yosuke Kakutsubata at Miyazaki Konan Hospital), and Data and Safety Monitoring Committee (Drs. Jin Takashiki at Nihon University, Keizo Horihara at Nagoya Medical Center, and Keitaro Matsuo at Aichi Cancer Center) and Ms. Fumiyu Ando for excellent technical support for real-time quantitative PCR assay.

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Received March 30, 2012; revised May 16, 2012; accepted May 17, 2012; published OnlineFirst June 6, 2012.

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4189

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Pretreatment EBV-DNA Copy Number Is Predictive of Response and Toxicities to SMILE Chemotherapy for Extranodal NK/T-cell Lymphoma, Nasal Type


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