Expression of nm23-H1 is associated with poor prognosis in peripheral T-cell lymphoma, not otherwise specified

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Running title: nm23-H1 expression in PTCL-NOS

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Statement of Translational Relevance.

There have been few reports on biological prognostic factors of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Therefore, there are few indexes that can be used to decide whether to perform autologous hematopoietic stem cell transplantation (AH SCT) after high-dose chemotherapy or only chemotherapies. Therefore, a study on nm23-H1 expression is important when treatment strategies such as AH SCT for nm23-H1 overexpression in PTCL-NOS are being considered. In addition, there are few effective treatments for PTCL-NOS at present. Therefore, for PTCL-NOS with high nm23-H1 expression, the development of treatments that target nm23-H1 and neighboring molecules is needed.
Abstract

Purpose: We examined whether nm23-H1 is a prognostic factor of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).

Experimental Design: We studied 102 consecutive, untreated PTCL-NOS patients from 1998 to 2008. The expression of nm23-H1 and TIA-1 was studied by immunohistochemistry.

Results: nm23-H1 was positive in 44.1%, and TIA-1 in 78.4% of the PTCL-NOS patients. nm23-H1 expression was not correlated with age, PS, LDH level, or stage, but was significantly correlated with the Prognostic Index for T-cell Lymphoma. The serum nm23-H1 level was 43.44 ng/ml in the cytoplasmic nm23-H1-strongly positive, 24.32 ng/ml in the cytoplasmic nm23-H1-moderately positive, and 13.64ng/ml in the cytoplasmic nm23-H1-negative patients. The nm23-H1-positive group had significantly shorter overall survival (OS). TIA-1 had no prognostic impact on five-year OS rates. OS was significantly shorter in patients with the following clinicopathologic features: age ≥ 60 years, PS of 2-4, LDH ≥ normal, bone marrow involvement, or nm23-H1-positive lymphoma. Multivariate analysis confirmed nm23-H1 expression to be an independent prognostic factor.

Conclusions: The nm23-H1 protein may be an important prognostic factor in PTCL-NOS. Because our results suggested that nm23-H1 is produced by lymphoma cells, we expect to see the development of new treatments targeting nm23 overexpression.

Key words: nm23; peripheral T-cell lymphoma, not otherwise specified; TIA-1
Introduction

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is relatively rare, accounting for only 10% to 15% of non-Hodgkin’s lymphomas (NHLs)\(^1\)\(^2\) and has heterogeneous clinical, histological, immunophenotypic, cytogenetic, and molecular features. The international prognostic index (IPI)\(^3\) is generally used as a prognostic factor. The IPI may be used in PTCL-NOS patients for risk stratification in order to identify patients for clinical trials. Recently, Gallamini et al.\(^4\) analyzed patients with PTCL-NOS and proposed a new prognostic index for T-cell lymphoma including age, performance status (PS), lactate dehydrogenase (LDH) level, and bone marrow involvement. This Prognostic Index for T-cell Lymphoma (PIT) model was able to identify four groups of patients with different outcomes, and had overall superior predictive capacity compared with the IPI.

nm23-H1 was originally identified as a protein that was expressed at a lower level in metastatic cancer cells. The nm23 genes play critical roles in cellular proliferation, differentiation, oncogenesis, and tumor metastasis. We previously established an enzyme-linked immunosorbent assay (ELISA) technique for determination of the serum level of nm23-H1 protein\(^5\)\(^6\), and reported that the serum level of nm23-H1 in patients with aggressive lymphoma was significantly higher than that in healthy controls, and that a high nm23-H1 level was associated with poor prognosis in aggressive lymphoma\(^5\). In our previous immunohistochemical study on cytoplasmic nm23-H1 expression in diffuse large B-cell lymphoma (DLBCL), we found that patients with positive cytoplasmic staining had significantly poorer prognosis than patients with negative staining\(^7\).

In this study, our first purpose was to examine nm23-H1 expression in PTCL-NOS in order to evaluate whether lymphoma cells produce the protein. Our second purpose was to examine the clinical significance of cytotoxic molecules such as TIA-1, and nm23-H1 expression in PTCL-NOS.

Patients and Methods

Patients
We studied 102 consecutive, untreated PTCL-NOS patients who were managed by the Adult Lymphoma Treatment Study Group (ALTSG) in Japan from 1998 to 2008. All patients were newly diagnosed, were previously untreated, and received anthracycline-containing combination chemotherapy. Briefly, the CyclOBEAP [cyclophosphamide (CPA), vincristine (VCR), bleomycin, etoposide, doxorubicin (DXR), prednisone (PDN)] regimen \(^8\) was primarily administered to younger patients (\(\leq 69\) years old) with PTCL-NOS, and the CHOP (CPA, DXR, VCR, PDN) regimen was primarily administered to older patients (>70 years old). The median follow-up time was 76 months (range: 28 to 122 months).

**Morphological and immunophenotypic studies**

Histological analysis of the materials from each patient was performed independently by six pathologists from the ALTSG. Lymphomas were classified according to the 4th World Health Organization (WHO) classification by the committee pathologists.\(^9\)

The expression of nm23-H1 and TIA-1 by lymphoma cells was examined immunohistochemically on formalin-fixed, paraffin-embedded sections by the avidin-biotin-peroxidase complex method.\(^7\)\(^10\) Monoclonal antibodies to nm23-H1 [clone 37.6, Novocastra Laboratories, Ltd, Newcastle upon Tyne, UK; clone H1-229, Seikagaku Corporation, Tokyo, Japan] was used as primary reagents. Working dilutions of these antibodies and tissue distribution of positive cells were checked by using lymph nodes with reactive hyperplasia. Consequently, clone 37.6 among the above antibodies gave satisfactory staining at a range of 1:50 to 1:200 dilutions. Monoclonal antibodies to TIA-1 (Immunotech, Marseille, France) were used to detect cytotoxic cell-associated proteins.

The following categories were defined for TIA-1 expression: negative (<30% positively-stained tumor cells) and positive (>30% positively-stained tumor cells). The following categories were defined for nm23-H1 expression: negative (<30% positively-stained tumor cells), low-to-medium positive (30\(\sim\)50% positively-stained tumor cells), and strongly positive (>50% positively-stained tumor cells).

The rates of cells positive for nm23-H1 or TIA-1 per proliferating fraction were determined by six hematopathologists who constituted the ALTSG Pathology Review Board (five are acknowledged and the remaining is one of the authors, H.N.).
were first determined independently by each pathologist, and the results were later discussed and verified by all of the pathologists using a multi-headed microscope and TV monitors at the time of the ALTSG Central Review Meeting for the diagnosis of lymphoma cases.

**ELISA for determination of the serum nm23-H1 level**

We previously established an ELISA procedure to determine the nm23-H1 protein level in the serum. 5) Briefly, 96-well plates (Corning Co., Corning, NY, USA) were coated with a monoclonal anti-nm23-H1 antibody (Seikagakukougyo Co., Tokyo, Japan), washed four times with PBS, and incubated with 25% Block Ace solution (Dainihon Seiyaku, Osaka, Japan). Serum samples were diluted two-fold with PBS and 50-µl aliquots were added to the wells. After incubation at room temperature for 1 h, the wells were washed four times with PBS containing 0.05% Tween 20 (T-PBS). Samples were then incubated at room temperature for 1 h with a polyclonal rabbit anti-nm23-H1 antibody (Santa Cruz Biotechnologies Inc., Santa Cruz, CA, USA), washed four times with T-PBS, and incubated with alkaline phosphatase-conjugated anti-rabbit IgG (BioRad Lab, Richmond, CA, USA). After four washes with T-PBS, alkaline phosphatase activity was detected with diethanolamine as a substrate and an alkaline phosphatase-detection kit (BioRad Lab). The reaction was stopped with 50 µl of 0.4 N NaOH. Absorbance was measured at 405-415 nm with a correction wavelength of 620-630 nm using a microplate reader.

**Statistical analyses**

Differences in characteristics between the two groups were examined by the $\chi^2$ test, Fisher’s exact test, and Mann-Whitney-U test, and $p<0.05$ was taken to indicate significance. Judgment criteria used for the analysis were progression-free survival (PFS) and overall survival (OS). Progression was defined as: progression of the lymphoma in nonresponding patients and in partial response patients; a relapse in
complete response patients; or death from any cause without progression. PFS was calculated as the duration from the date of beginning chemotherapy to the date of progression or relapse or to the date of the last contact. Survival analysis was performed according to the Kaplan-Meier method. The statistical significance of the differences in survival was determined by the log-rank test. Multivariate analysis of the prognosis was performed using Cox's proportional-hazards regression model. All statistical analyses were performed with SAS software (version 9, SAS Institute, Cary, NC, USA).

Results

nm23-H1 and TIA-1 expression in mature T-cell lymphoma

Eighty-four (45.7%) of 184 patients with mature T-cell lymphoma in the ALTSG from 1998 to 2008 were positive for nm23-H1 (Fig.1). In 53 patients (28.8%), more than 70% of the lymphoma cells expressed nm23-H1, while in the remaining 31 patients (16.8%), 30-69% of the lymphoma cells were stained. The frequencies of positivity for nm23-H1 expression according to lymphoma subtype were: 45 (44%) of 102 patients with PTCL-NOS, 20 (38%) of 52 patients with angioimmunoblastic T-cell lymphoma (AITL), and 19 (63%) of 30 patients with anaplastic large cell lymphoma (ALCL). A significantly higher proportion of ALCL cases were positive for nm23-H1 expression compared with PTCL-NOS (P=0.031) and AITL cases (P=0.015). On the other hand, 41 (22%) of 184 patients with mature T-cell lymphoma were positive for TIA-1. The frequencies of positivity for TIA-1 according to lymphoma subtype were: 22 (21.6%) of 102 patients with PTCL-NOS, 15 (28.8%) of 52 patients with AITL, and 4 (13.3%) of 30 patients with ALCL. As for the expression of TIA-1, there was no significant difference in positivity of TIA-1 among the three T-cell lymphoma subtypes.

Relationship between nm23-H1 or TIA-1 expression and clinical characteristics in patients with PTCL-NOS

The relationship between nm23-H1 or TIA-1 expression and clinicopathological
factors was investigated in the 102 patients with PTCL-NOS (Table 1). There were no correlations between nm23-H1 expression and age, performance status (PS), serum LDH level, stage, or bone marrow involvement, but a significantly higher percentage of patients with a high prognostic index for T-cell lymphoma (PIT) score showed nm23-H1 expression (P=0.005). The nm23-H1-positive rate among the patients who achieved complete response (CR) was 34.8%, while the nm23-H1-positive rate among those who failed to do so was 61.1%, the difference being statistically significant (p=0.004). Thus, a close relationship between cytoplasmic nm23-H1 expression and therapeutic responsiveness was found. Similarly, there were no correlations between TIA-1 expression and age, performance status (PS), serum LDH level, stage, bone marrow involvement, PIT score, and CR rate.

**Survival in patients with PTCL-NOS**

Among the 102 PTCL-NOS patients, the 5-year OS and PFS rates were 51.5% and 35.7%, respectively. The patients were divided into 3 groups according to the level of nm23-H1 expression. The 5-year OSs of the patients with negative (n = 57), low-to-medium positive (n = 15), and strongly positive (n = 30) nm23-H1 expression were 71.3%, 31.7%, and 24.1%, respectively, and there was a correlation among the three groups by the log-rank test (p=0.0004) (Fig. 2A). PFS was examined in a similar manner. The 5-year PFSs among patients with negative, low-to-medium positive, and strongly positive staining were 57.7%, 12.7%, and 8.5%, respectively. The log-rank test revealed a significant correlation among the three groups (p=0.0003) (Fig. 2B). The patients were divided into 2 groups according to the presence or absence of TIA-1 expression. The 5-year OS rate of the TIA-1- negative and -positive groups was 40.5% (n=80) and 51.6% (n=22), respectively (p=0.37), showing no significant difference (Fig. 3A). The 5-year PFS rate of the TIA-1-negative and -positive groups was 40.5% (n=80) and 51.8% (n=22), respectively (p=0.32), showing no significant difference (Fig. 3B).

When the patients were classified according to the PIT, the 5-year OS of group 1 and 2
(n = 43) was 56.5% and that of group 3 and 4 (n = 59) was 40.2%, showing no significant difference (p = 0.055). The 5-year PFS of group 1 and 2 (n = 43) was 55.1% and that of group 3 and 4 (n = 59) was 37.3%, showing no significant difference (p = 0.09). Further evaluation of the 5-year OS and PFS among the patients according to the IPI showed that the 5-year OS in patients with L-I, H-I or H risk was 57%, 52% and 28%, respectively (P=0.08), and the 5-year PFS in patients with L-I, H-I or H risk was 54%, 50% and 26%, respectively (P=0.14) (data not shown).

CyclOBEAP therapy was administered to 48 PTCL-NOS patients. The 5-year OS rate was 68% and 5-year PFS rate was 56%. On the other hand, CHOP therapy was administered to 54 patients. The 5-year OS rate was 38% and 5-year PFS rate was 31%. In both therapies, nm23-H1 overexpression >50% tumor cells stained was significantly associated with poor prognosis.

**Significance of nm23-H1 expression in the OS and PFS of patients in various PIT groups**

We evaluated the significance of nm23-H1 expression in PTCL-NOS among patients classified according to the PIT. In group 1 and 2, OS (Fig. 4A) was worse among patients who were positive for nm23-H1 (n=19, 5-year OS; 32.4%) than among those who were negative for nm23-H1 (n=24, 5-year survival; 75.9%) (P=0.006), indicating that the therapeutic outcome was worse with nm23-H1 expression. The prognosis of patients who were positive for nm23-H1 was also poor in group 3 and 4 (P=0.0001) (Fig. 4B). We examined the PFS with nm23-H1 expression levels and obtained the following results: in group 1 and 2, 19 patients were positive for nm23-H1 (5-year PFS 35.5%) and 24 patients were negative for nm23-H1 (5-year PFS 71.7%) (Fig. 4C); in group 3 and 4, 26 patients were positive for nm23-H1 (5-year PFS 19.8%) and 32 patients were negative for nm23-H1 (5-year PFS 50.4%) (Fig. 4D). The PFS prognosis of patients with high nm23-H1 was poor in all of these risk groups (p=0.0001). Therefore, we might be able to predict the therapeutic outcome in each PIT risk group of PTCL-NOS using nm23-H1 expression at diagnosis.

**Comparison between serum nm23-H1 level and cytoplasmic nm23-H1 expression in**
**PTCL-NOS**

The serum nm23-H1 level in 30 patients with cytoplasmic nm23-H1-strongly positive PTCL-NOS was $43.44 \pm 21.48 \text{ ng/ml (mean } \pm \text{ SD)}$, that in 15 patients with cytoplasmic nm23-H1-low-to-medium positive PTCL-NOS was $24.32 \pm 22.11 \text{ ng/ml}$, and that in 57 patients with cytoplasmic nm23-H1 negative PTCL-NOS was $13.64 \pm 11.62 \text{ ng/ml}$. Although there was no significant difference in the serum nm23-H1 level between the patients with negative staining and those with low-to-medium positive staining ($p = 0.058$), there were significant differences between the patients with strongly positive staining and those with moderately positive staining ($p = 0.029$) and also between those with strongly positive staining and those with negative staining ($p = 0.0001$) (Fig. 5). Therefore, this result suggests that a portion of the serum nm23-H1 had been produced directly by lymphoma cells.

**Univariate and multivariate analyses of OS and PFS in patients with PTCL-NOS**

OS was significantly shorter in patients with the following clinicopathologic features: age over 60 years, PS of 2-4, LDH>normal, bone marrow involvement, and nm23-H1-positive lymphoma. PFS was significantly shorter in patients with the following clinicopathologic features: age over 60 years, LDH>normal, bone marrow involvement, and nm23-H1-positive PTCL-NOS. Multivariate analysis with these individual factors showed nm23-H1 expression (hazards ratio, 6.09, 95% CI, 2.85 to 17.21; $p=0.0001$) and bone marrow involvement (hazards ratio, 3.31, 95% CI, 0.23 to 12.87; $p=0.032$) to be significant and independent prognostic factors among the 102 PTCL-NOS patients (Table 2).

**Discussion**

PTCL-NOS is more aggressive and has a poorer prognosis than DLBCL. The treatment strategy for PTCL-NOS at present is generally determined by the IPI and PIT. By using the IPI and PIT, a fairly accurate prognostication could be made and, hence, it would be possible to make a stratified treatment plan for each patient. However, IPI and PIT are markers based primarily on clinical findings and laboratory data. In the
present study, when the patients were classified according to the PIT, the 5-year OS and PFS of group 1 and 2 and those of group 3 and 4 showed no significant differences. Therefore, treatment strategies stratified by a new prognostic factor are necessary. Recently, prognostic factors for PTCL-NOS based on the biological characteristics of tumor cells have been identified. TIA-1 is a 15-kD cytotoxic granule-associated protein that is structurally related to the tumor necrosis factor receptor family; TIA-1 induced apoptotic cell death when introduced into permeabilized target cells.\(^{11}\) Cytotoxic cell-associated molecules, such as TIA-1, are primarily expressed in cytotoxic T cells and natural killer cells. TIA-1 moves to the cytoplasm through the perforin-formed pore and activates apoptosis-associated protein. TIA-1 was originally recognized as a protein that directly induces apoptosis of target cells and is present in azurophilic cytoplasmic granules of T lymphocytes. TIA-1, however, is expressed in cytotoxic T cells, regardless of their activation status, and in myeloid cells.\(^{12}\) Asano et al.\(^ {13}\) identified that expression of cytotoxic antigens in T-cell lymphoma cells may represent a poor prognostic factor in PTCL-NOS. In the present study, TIA-1 was expressed in 22 % of PTCL-NOS tumors, and there were no significant differences in OS and PFS between the TIA-1-positive group and the TIA-1-negative group.

On the other hand, the \textit{nm23} gene was initially identified as a putative metastasis suppressor gene on the basis of its reduced expression in certain highly metastatic cell lines and tumors.\(^ {14}\) The level of \textit{nm23}-H1 expression was inversely correlated with the tumor’s metastatic potential in experimental rodent cells and in human tumors, such as ovarian, breast, and cervical tumors and melanomas.\(^ {15}\) On the contrary, the opposite trend has been reported in thyroid carcinoma, neuroblastoma and non-Hodgkin lymphoma, although the mechanism of this discrepancy is unknown.\(^ {5}-7,16\) We previously reported cytoplasmic \textit{nm23}-H1 expression in DLBCLs\(^ {7}\) and Hodgkin lymphomas,\(^ {10}\) and found that the serum and cytoplasmic \textit{nm23}-H1 levels were significant prognostic factors in both DLBCLs and Hodgkin lymphomas. In the present study, cytoplasmic \textit{nm23}-H1 expression in lymphoma cells was analyzed in 102 patients with PTCL-NOS. \textit{nm23}-H1 expression was not correlated with age, PS, LDH level, or stage, but was significantly correlated with PIT. Next, we examined the
relationship between nm23-H1 expression and OS and PFS. Patients with nm23-H1-positive PTCL-NOS had significantly shorter OS and PFS than those with nm23-H1-negative PTCL-NOS. OS was significantly shorter in patients with the following clinicopathologic features: age \( \geq 60 \text{ years} \), PS of 2-4, LDH \( \geq \) normal, bone marrow involvement, or nm23-H1-positive PTCL-NOS. Multivariate analysis confirmed nm23-H1 expression to be an independent prognostic factor.

nm23-H1 binding protein is a latent protein encoded by the Epstein-Barr virus (EBV) nuclear antigen 3C (EBNA 3C). EBV is a common human virus that is associated with a number of human cancers, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, and PTCL-NOS. 17) EBV is positive in approximately 30% of patients with PTCL-NOS, although its role in pathogenesis is unknown. 18) EBNA 3C, a transcription factor, interacts with nm23-H1, which results in enhanced transactivating activity. 17) In the present study, EBER was positive in 10 of the 26 PTCL-NOS patients in whom EBER ISH was performed, and nm23-H1 was positive in 5 of the 10 patients (data not shown). The number of PTCL-NOS patients will increase in the future, and to 'the role of EBER needs to be examined. On the other hand, nm23-H1 binding proteins include the T-cell lymphoma invasion and metastasis 1, a guanine nucleotide exchange factor for Rac1. 19) Rac1 was not examined in this study, but it is thought to be an important factor when the relationship between nm23-H1 and PTCL-NOS was examined.

On the other hand, we previously transplanted a human B-lymphocytic lymphoma cell line that overexpressed nm23-H1 into immunosuppressed nude mice and examined the tumor size and serum human nm23-H1 protein levels. nm23-H1 protein was detected in the serum of nude mice depending on the tumor size. These results strongly suggest that serum nm23-H1 protein is directly produced by lymphoma cells and its level depends on the total mass of malignant cells overexpressing nm23-H1. 20) In conclusion, the nm23-H1 protein may be an important prognostic factor in PTCL-NOS. Because our results suggested that nm23-H1 is produced by lymphoma cells, we expect to see the development of new treatments targeting nm23 overexpression.
Acknowledgments

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References


**Figure Legends**

**Figure 1.** Hematoxylin and eosin staining (A,B) and immunohistochemical staining for nm23 (C,D) of PTCL-NOS.

The nodal structure is largely obliterated by a diffuse process with occasional remaining atrophic lymph follicles on the left (A). The proliferating cells are medium-sized to large and have a considerable amount of cytoplasm (B). They are diffusely positive for nm23 (C), and cytoplasmic staining is evident at this higher magnification (D). A and B, H & E stain; C and D, Immunoperoxidase stain with hematoxylin counterstain. A and C, x10; B and D, x40.

**Figure 2.** Overall survival curve (A) and progression-free survival curve (B) of patients with peripheral T-cell lymphoma, not otherwise specified according to the expression of cytoplasmic nm23-H1.

**Figure 3.** Overall survival curve (A) and progression-free survival curve (B) of patients with peripheral T-cell lymphoma, not otherwise specified according to the expression of TIA-1.

**Figure 4.** Overall survival curve (A, B) and progression-free survival curve (C, D) of patients with peripheral T-cell lymphoma, not otherwise specified according to the Prognostic Index for T-Cell Lymphoma

A, C: Group 1 and 2; B, D: Group 3 and 4

**Figure 5.** Relationship between the serum nm23-H1 level and cytoplasmic nm23-H1 expression in PTCL, not otherwise specified
Table 1. Correlation of nm23-H1 with TIA-1 Expression and Prognostic Characteristics in Peripheral T-Cell Lymphoma, NOS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>nm23-H1(+) (n=45) (%)</th>
<th>P-value</th>
<th>TIA-1(+) (n=22) (%)</th>
<th>P-value</th>
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<tr>
<td>Age</td>
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<tr>
<td>≤60 years</td>
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<td>21 (45.7)</td>
<td>0.78</td>
<td>11 (23.9)</td>
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<td>&gt; 60 years</td>
<td>56</td>
<td>24 (42.9)</td>
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<td>11 (19.6)</td>
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<td>WHO performance status</td>
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<td>0, 1</td>
<td>64</td>
<td>26 (40.6)</td>
<td>0.36</td>
<td>13 (20.3)</td>
<td>0.67</td>
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<tr>
<td>2~4</td>
<td>38</td>
<td>19 (50)</td>
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<td>9 (23.6)</td>
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<td>&gt;Normal</td>
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<td>17 (21.2)</td>
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<td>Ann Arbor stage</td>
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<td>I, II</td>
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<td>12 (50)</td>
<td>0.51</td>
<td>6 (25)</td>
<td>0.64</td>
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<td>III, IV</td>
<td>78</td>
<td>33 (42.3)</td>
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<td>16 (20.5)</td>
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<td>Bone marrow involvement</td>
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<td>Absent</td>
<td>81</td>
<td>33 (40.7)</td>
<td>0.18</td>
<td>19 (23.4)</td>
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<td>Present</td>
<td>21</td>
<td>12 (57.1)</td>
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<td>3 (14.3)</td>
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<td>Prognostic index for T-cell lymphoma (PIT)</td>
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<td>Group 1/2</td>
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<td>15 (34.9)</td>
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<td>11 (23.9)</td>
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<td>Group 3/4</td>
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<td>30 (50.8)</td>
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<td>11 (19.6)</td>
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<td>Therapeutic effect</td>
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<td>Complete response</td>
<td>66</td>
<td>23 (34.8)</td>
<td>0.004</td>
<td>18 (27.3)</td>
<td>0.06</td>
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<td>Non-complete response</td>
<td>36</td>
<td>22 (61.1)</td>
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<td>4 (11.1)</td>
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Fig. 2

A. Overall survival

- Negative (n=57)
- Low-to-medium (n=15)
- Strong (n=30)

B. Progression-free survival

- Negative (n=57)
- Low-to-medium (n=15)
- Strong (n=30)

P-values:

- A: P=0.0004
- B: P=0.0003
Fig. 3

A. Overall survival

B. Progression-free survival

TIA-1 (+)

TIA-1 (-)

P = 0.37

P = 0.32

Month

TIA-1 (+)

TIA-1 (-)

0 12 24 36 48 60 72 84 96 108 120

0 50 100

0 12 24 36 48 60 72 84 96 108 120

0 50 100
Fig. 4

Overall survival
A. Group 1/2

nm23(-)  P=0.006
nm23(+)  

B. Group 3/4

nm23(-)  P=0.0001
nm23(+)  

Progression-free survival
C. Group 1/2

nm23(-)  P=0.005
nm23(+)  

D. Group 3/4

nm23(-)  P=0.0001
nm23(+)  

nm23(-)

nm23(+)
Concentration of nm23-H1 (ng/ml)

- nm23-H1 negative (n=57)
- nm23-H1 Low-to-medium (n=15)
- nm23-H1 strong (n=30)

P-values:
- P=0.0001
- P=0.058
- P=0.029

Fig. 5
Table 2. Multivariate Analysis of Prognostic Factors in Peripheral T-cell Lymphoma, NOS

<table>
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<tr>
<th>Covariate</th>
<th>Covariate sub-group</th>
<th>Hazards Ratio</th>
<th>95%CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nm23-H1</td>
<td>positive</td>
<td>6.09</td>
<td>2.85 to 17.21</td>
<td>0.0001</td>
</tr>
<tr>
<td>BM involvement</td>
<td>present</td>
<td>3.31</td>
<td>0.23 to 12.87</td>
<td>0.032</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>&gt;Normal</td>
<td>1.51</td>
<td>0.85 to 4.41</td>
<td>0.45</td>
</tr>
<tr>
<td>Performance status</td>
<td>2~4</td>
<td>1.46</td>
<td>0.76 to 6.62</td>
<td>0.56</td>
</tr>
<tr>
<td>Age</td>
<td>≥60 years</td>
<td>2.12</td>
<td>0.60 to 10.24</td>
<td>0.63</td>
</tr>
</tbody>
</table>

CI, confidence interval; BM, bone marrow
Expression of nm23-H1 is associated with poor prognosis in peripheral T-cell lymphoma, not otherwise specified

NOZOMI NIITSU, Hirokazu Nakamine and Masataka Okamoto

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