Effect of Positive Bone Marrow EBV *In situ* Hybridization in Staging and Survival of Localized Extranodal Natural Killer/T-Cell Lymphoma, Nasal-Type

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Abstract

Purpose: The aim of the study was to determine the effect of EBV-encoded RNA-1 *in situ* hybridization (EBER-1 ISH) in bone marrow specimens on survival outcome in patients with clinical stage I/II natural killer/T-cell lymphoma.

Experimental Design: We systematically did EBER-1 ISH on 182 archival bone marrow tissues from 91 patients who were diagnosed of stage I/II natural killer/T-cell lymphoma and analyzed the correlation between bone marrow EBER-1 ISH status and survival. We defined minimal bone marrow involvement and definite bone marrow involvement to distinguish the subgroups who revealed EBV-positive cells from normal marrow by EBER-1 ISH from those who showed typical neoplastic cells in bone marrow biopsies.

Results: In total, 17 of the 91 (18.7%) patients showed positivity for EBER-1 ISH at least in one of the bilateral bone marrow biopsies with 14 minimal bone marrow involvements and 3 definite bone marrow involvements. Patients with positive bone marrow EBER-1 ISH showed significantly poorer overall survival than those who were negative for bone marrow EBER-1 ISH (median survival, 16.1 months versus not reached; $P = 0.045$).

Conclusion: Considering a high proportion of stage I/II patients (15.4%) with minimal in bone marrow specimens, bone marrow EBER-1 ISH should be routinely done in all patients with localized disease for more accurate staging.

It is known that the frequency of bone marrow involvement is relatively low in natural killer (NK)/T-cell lymphomas compared with other subsets of lymphomas. Previous reports, including ours, have shown that the bone marrow involvement based on morphologic examination is <10% in nasal NK/T-cell lymphomas (1–6). For stage I/II nasal NK/T-cell lymphomas, primary chemotherapy and/or radiotherapy provided complete remission rates of 40% to 60% with 5-year overall survival rates of 42% to 83% (7–13). One of the plausible explanation that may account for such unsatisfactory survival outcome for localized disease with a relatively high systemic failure rate of 25% to 30% (7–9, 14) is an unrevealed dissemination of lymphoma cells at the time of diagnosis. In our preliminary report, the incidence of minimal bone marrow involvement detected by EBV *in situ* hybridization (ISH) was 5% (2 of 30) and these patients had poor prognosis (6). Enhancing the sensitivity of detection methods by using immunoglobulin or T-cell receptor gene rearrangement revealed occult lymphoma cells from morphologically normal marrow in several other non–Hodgkin's lymphomas (15–17). Although the role of EBV infection in pathogenesis of NK/T-cell lymphomas needs to be refined, it is well recognized that the presence of EBV is essential in carcinogenesis of NK/T-cell lymphoma. ISH for EBV-encoded RNA-1 (EBER-1) has been a powerful tool to identify NK lymphoma cells in histopathologic sections (18).

Therefore, we retrospectively did EBER-1 ISH on archival bone marrow tissues from 91 patients with localized nasal NK/T-cell lymphoma to assess the correlation between EBER-1 ISH positivity of the bone marrow and staging as well as survival outcome. In this study, the pattern of bone marrow infiltration was categorized into two subgroups: definite bone marrow involvement versus minimal bone marrow involvement.

Materials and Methods

Patient selection. From October 1995 to June 2005, 91 patients were identified to satisfy the following criteria: (*a*) pathologically confirmed diagnosis of NK/T-cell lymphoma according to WHO

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Note: J. Lee and C. Suh contributed equally to this work.

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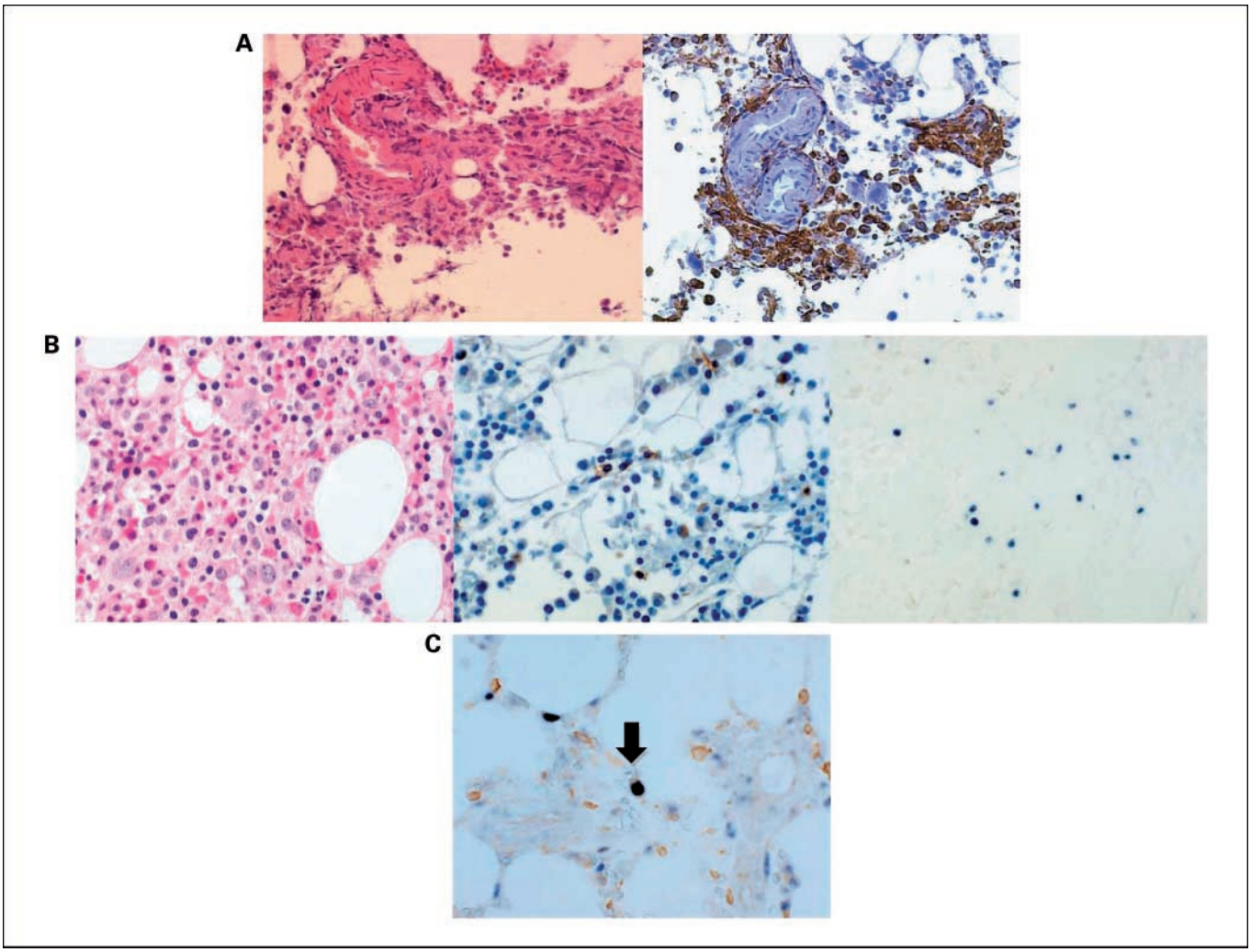

Fig. 1. Results of EBER-1 ISH in bone marrow specimens. *A,* definite bone marrow involvement shows perivascular infiltration of CD3-positive atypical cells. *Left,* H&E staining. Magnification, ×40. *Right,* immunohistochemical staining for CD3. Magnification, ×40. *B,* minimal bone marrow involvement shows normocellular bone marrow with three-lineage hematopoiesis without the presence of apparent atypical cells in H&E staining (*left*), few CD3-positivie small cells (*middle*), but several EBER-1 – positive small lymphoid cells on EBER-1 ISH (*right*). *C,* the double procedure for ISH with EBER-1 probe and immunohistochemistry for CD3ε confirmed that the EBER-1 – positive cells are also positive for CD3ε.

classification; (*b*) localized disease, stage I or II, according to the Ann Arbor classification; (*c*) localized disease with isolated involvement of bone marrow without spread to any other organs; and (*d*) availability of bilateral bone marrow specimens obtained at the time of diagnosis for review. Extranasal NK/T-cell lymphoma was defined as described previously (13). Briefly, upper aerodigestive tract NK/T-cell lymphoma (UNKTL) was defined as those involving nasal cavity, nasopharynx, and the upper aerodigestive tract, whereas extra-UNKTL embraced lymphomas occurring at all other sites (13). In this study, patients with extra-UNKTL or with disseminated UNKTL (except for those with isolated bone marrow involvement) were excluded from the analysis. The following clinical data were collected from the record: patient demographics, complete blood count, lactate dehydrogenase level, Ann Arbor stage, International Prognostic Index (IPI), NK/T-cell lymphoma IPI, the presence of B symptoms, performance status, date of diagnosis, bone marrow findings, date of last follow-up, vital status, and cause of death. NK/T-cell lymphoma IPI was reported in our previous study (1). Briefly, NK/T-cell lymphoma IPI consists of the presence of B symptoms, stage, elevated lactate dehydrogenase, and regional lymph nodes (N_1-N_3) according to the tumor-node-metastasis system.

Bone marrow specimens and histology. In all cases, all smear and trephine biopsy specimens of the bone marrow were retrieved for review and further studies. All patients had bilateral specimens of the bone marrow for review. All H&E-stained bone marrow biopsies and smears were thoroughly reviewed by two pathologists (Y.H.K. and J.H.) for the presence of malignant cells. The bone marrow biopsy sections were stained with polyclonal antibody for CD3 (1:200; Novocastra), monoclonal antibody for CD20 (1:500; Novocastra), and monoclonal antibody for CD56 (1:20; Monosan). EBV RNA was detected by an ISH technique. A simultaneous labeling method using EBER-1 ISH and immunohistochemistry for CD20 and CD3ε was done to differentiate lymphoid subsets of EBV-infected cells from malignant cells. Paraffin sections were pretreated with xylene followed by treatment with proteinase K and hybridized with FITC-conjugated EBV oligonucleotides (Novocastra) complementary to the nRNA portion of the *EBER-1* and *EBER-2* genes (5). Bone marrow was considered as positive for EBV ISH when there was at least more than one cell showing explicit nuclear staining with EBV oligonucleotide. As negative controls, EBV-negative lymphoid tissues and the hybridization mixture without the EBV oligonucleotides were used. In this study, patterns of bone marrow involvement were categorized into two subtypes: definite bone marrow

involvement and minimal bone marrow involvement. The definite bone marrow involvement was defined as the presence of unequivocal malignant lymphoid cells in bone marrow, which is confirmed by H&E stain and immunohistochemistry for CD3.

Treatment. Patients received one of the following initial treatment: (*a*) cyclophosphamide-Adriamycin-vincristine-prednisone with or without involved-field radiotherapy; (*b*) dose-escalated cyclophosphamide-Adriamycin-vincristine-prednisone; (*c*) ifosfamide, methotrexate, etoposide; (*d*) dexamethasone, cytarabine, cisplatin; (*e*) etoposide, ifosfamide, cisplatin, dexamethasone with or without involved-field radiotherapy; (*f*) etoposide, methylprednisolone, cisplatin, cytarabine; or (*g*) involved-field radiotherapy alone.

Statistical analysis. Categorical variable in two groups was compared by the χ^2 test, whereas continuous variables were analyzed by Student's *t* test. *P* values of <0.05 were considered statistically significant. Overall survival was estimated using the Kaplan-Meier product-limit method. Overall survival was measured from the date of diagnosis to the date of death or the last follow-up visit. Survival rates were compared for statistical differences by using log-rank analysis.

Results

EBER-1 ISH and immunohistochemical studies. A representative pathologic finding of definite bone marrow involvement is shown in Fig. 1A, which shows perivascular infiltration of the CD3-positive neoplastic cells. The minimal bone marrow involvement was defined as the absence of unequivocal neoplastic cells in bone marrow by H&E stain and immunohistochemistry for CD3 but the presence of EBV-stained cells by EBER ISH. Figure 1B shows normocellular bone marrow with three-lineage hematopoiesis without the presence of apparent atypical cells in H&E staining but several EBER-1–positive small lymphoid cells on EBER-1 ISH. Figure 1C illustrates a double-stained malignant cell with EBER-1 ISH and CD3ε.

In total, 17 of the 91 (18.7%) patients showed positivity for EBER-1 ISH in one of the bilateral bone marrow biopsies. Five (29.4%) patients had unilateral bone marrow EBER-1 ISH positivity and 12 (70.6%) patients had bilaterally positive results for EBER-1 ISH. Consequently, 29 (15.9%) bone marrow specimens of the 182 bone marrows examined were positive for EBER-1 ISH in this study (Fig. 2). Fourteen patients with localized NK/T-cell lymphoma had minimal bone marrow involvement and only 36 patients showed definite bone marrow involvement (positive neoplastic cells in H&E stain and immunohistochemical study for CD3; Fig. 1). All of the 15 patients with minimal or definitive bone marrow involvement had EBV-positive primary tumors, whereas 2 patients did not have information on the EBV status of the primary lesion. The number of cells with EBER-1 ISH positivity in minimal bone marrow involvement was distributed as follows: single positive cell, $n = 1$; few positive cells (less than five), $n = 11$; and numerous positive cells (more than five), $n = 2$. Of the 14 specimens with minimal bone marrow involvement, double labeling of the bone marrow section was successful in 5. Some EBER-positive cells were positive for CD3ε (Fig. 1C), and few EBER-positive cells that were negative for CD3ε were also negative for CD20. Additionally, there was no EBER-positive B cells observed in the stained specimens. All three patients with definite bone marrow involvement showed positive EBER-1 ISH in their bone marrows as well as the microscopic presence of neoplastic cells, and all were thus staged as Ann Arbor stage IV due to the isolated bone marrow involvement with local confinement of the primary lesion. The clinical manifestations, such as pancytopenia and/or hemophagocytosis, were not prominently detected in patients with definite or minimal bone marrow involvement. For this subset of patients, the median hemoglobin level was 11.9 g/dL, WBC count was 6,310/μL, absolute neutrophil count was 4,312/μL, and median platelet count was 210 K/μL. The hemophagocytosis was observed in bone marrow of 2 (11.8%) patients. Importantly, baseline characteristics of the patients with minimal bone marrow involvement did not significantly differ from those without bone marrow involvement with statistical significance (Table 1).

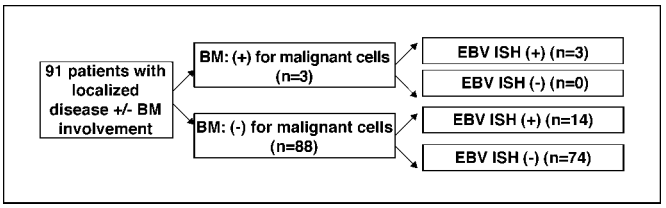

Fig. 2. Proportions of EBER-1 ISH positivity in localized NK/T-cell lymphoma. BM, bone marrow.

Survival according to the EBV status of the bone marrow. After a median follow-up duration of 39 months, the median survival of all patients has not been reached, with a 5-year overall survival of 61.9%. At the time of analysis, 30 (33.0%) patients were dead. Patients with positive bone marrow EBER-1 ISH showed significantly poorer overall survival than those who were negative for bone marrow EBER-1 ISH [median survival, 16.1 months (95% confidence interval, 6.4-25.8) versus not reached; $P = 0.045$; Fig. 3]. Notably, localized NK/T-cell lymphoma patients with minimal or definite bone marrow involvement showed continuous decline in survival, whereas the EBV-negative patients reached a plateau in their survival curves after ~2 years from diagnosis. Of the 17 bone marrow EBER-positive patients, 5 (29.4%) patients achieved complete remission after initial treatment. Of the five patients with complete remission, two (40.0%) patients relapsed at 2.0 and 3.7 months both with distant relapses. Of the five patients with initial partial remission, two (40.0%) patients developed systemic progression. The distributions of initial anthracycline-based chemotherapy or involved-field radiotherapy did not differ among the patients with or without minimal bone marrow involvement ($P = 0.137$ and 0.338, respectively).

Discussion

This study currently represents the largest one to evaluate the significance of bone marrow EBER-1 positivity by ISH on stage and survival outcome of localized NK/T-cell lymphoma patients. Few studies have limitedly speculated a putative role of bone marrow EBER-1 ISH on staging of NK/T-cell lymphoma due to small number of cases. In an attempt to elucidate the clinical implication of detecting occult lymphoma cells by EBER-1 ISH on stage-based stratification of therapy, we systematically did EBER-1 ISH in 182 bone marrow specimens from 91 patients with clinically localized NK/T-cell lymphoma. Using EBER-1 ISH technique, 14 (15.4%) patients had minimal bone marrow involvement and 3 (3.3%) patients showed definite bone marrow involvement.

Table 1. Patient characteristics according to the EBER-1 ISH status

Characteristics	Definite BM involvement (n = 3), n (%)	Minimal BM involvement (n = 14), n (%)	No BM involvement (n = 74), n (%)	P*
Age, >60	2 (66.7)	3 (21.4)	15 (20.3)	0.922
Male sex	3 (100.0)	12 (85.7)	45 (60.8)	0.074
Ann Arbor stage				
I	0 (0.0)	9 (64.3)	46 (62.2)	0.662 †
II	0 (0.0)	5 (35.7)	28 (37.8)	
IV	3 (100.0)	0 (0.0)	0 (0.0)	
Elevated LDH	3 (100.0)	4 (28.6)	27 (36.5)	0.570
IPI				
Low-low intermediate	0 (0.0)	13 (92.9)	73 (98.6)	0.440
High intermediate-high	3 (100.0)	1 (7.1)	1 (1.4)	
B symptom				
Yes	3 (100.0)	6 (42.9)	18 (24.3)	0.153
Initial anthracycline-based chemotherapy	2 (66.7)	9 (64.3)	59 (79.7)	0.137
Initial involved-field radiotherapy	0 (0.0)	8 (57.1)	32 (43.3)	0.338
NK/T-cell lymphoma IPI				
Group 1-2	0 (0.0)	9 (64.3)	54 (73.0)	0.458
Group 3-4	3 (100.0)	5 (35.7)	19 (25.7)	

NOTE: These patients had localized disease with bone marrow involvement only.
Abbreviations: BM, bone marrow; LDH, lactate dehydrogenase.
*P value for statistical comparison between the minimal bone marrow involvement versus no bone marrow involvement.
† Ann Arbor stage I/II versus IV.

Most importantly, localized NK/T-cell lymphoma patients with bone marrow EBER-1 ISH positivity showed survival outcome comparable with that of the disseminated UNKTL patients rather than the localized UNKTL patients (5-year overall survival for localized UNKTL without bone marrow EBER-1, 66.1%; for localized UNKTL, 76%; for localized UNKTL with bone marrow EBER-1 positive, 39%; for disseminated UNKTL, 28%; Fig. 3; refs. 1, 19). The survival curve of the localized UNKTL with bone marrow EBER-1 ISH positive did not reach plateau, whereas that of the bone marrow EBER-1 ISH negative plateaued after ~2 years. Despite of similar treatments given in the two groups, EBV-positive patients did significantly poorer in terms of survival. Notably, the baseline characteristics of patients with minimal bone marrow involvement were similar to those without EBV bone marrow involvement (Table 1) but still had tendency to pursue poorer outcome with relatively high rate of systemic relapse. These findings strongly suggest that this subgroup of patients should be identified early and be treated as aggressively as stage IV patients. Due to the small number of patients with definite bone marrow involvement (n = 3), it is difficult to compare clinical features or prognosis with those with minimal bone marrow involvement based on our data.

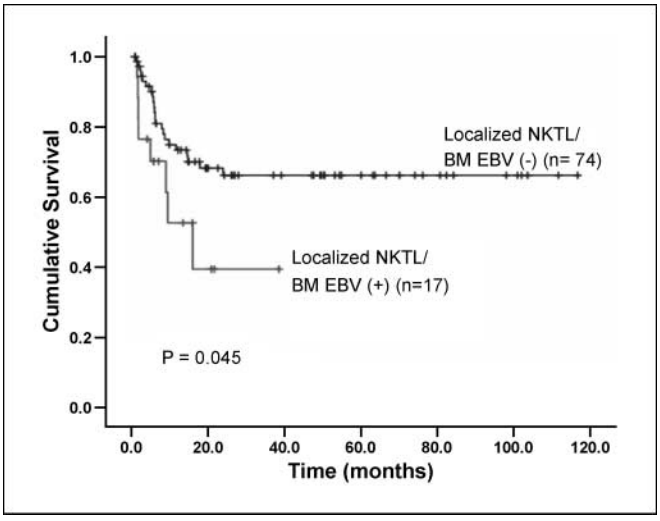

Fig. 3. Survival according to bone marrow EBER-1 ISH positivity.

We defined minimal bone marrow involvement and definite bone marrow involvement to distinguish the subgroups who revealed EBV-positive cells from normal marrow by EBER-1 ISH from those who showed typical neoplastic cells in the bone marrow biopsy specimens. To differentiate EBV-positive lymphoma cells from nonspecific EBV-positive B cells, such as memory B cells, from persistent EBV infection, we attempted to confirm malignant cells by simultaneous labeling using EBER-1 ISH and CD3ε/CD20. Although CD56 staining is known to have a high sensitivity in identifying malignant NK/T lymphoma cells, we did CD3ε staining due to technical difficulties for CD56 staining following decalcification of the bone marrow specimen. As stated in Results, we succeeded a simultaneous EBER ISH and immunohistochemistry using CD3ε and CD20 in 5 of 14 patients with minimal bone marrow involvement and showed that EBER-positive cells were positive for CD3ε or that these cells were not positive for CD20.

Recently, Kwong et al. (20) have shown that the level of circulating EBV DNA is correlated with disease stage and survival, reflecting the tumor load, leading to a conclusion that plasma EBV DNA can be used as a tumor biomarker to monitor treatment response. They hypothesized that the increase of EBV DNA was due to tumor release of EBV fragments rather than reactivation of latent EBV infection because NK/T-cell lymphoma patients are immunocompetent. Future analysis on the

association between the level of plasma EBV DNA and the EBER-1 ISH in bone marrow should be conducted.

Of the 17 patients with either definite or minimal bone marrow involvement, 6 patients underwent ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for staging evaluation; none of which suggested malignant involvement of bone marrow. The usefulness of ^{18}F-FDG PET in the detection of bone marrow involvement has been investigated in malignant lymphoma. One study compared bone marrow biopsy of the iliac crest and PET in 106 lymphoma patients and found that ^{18}F-FDG PET was more sensitive (86%) than bone marrow biopsy (57%; ref. 21). However, recent meta-analysis showed that the estimated sensitivity and specificity of bone marrow biopsy were 51% (95% confidence interval, 38-64%) and 91% (95% confidence interval, 85-95%), respectively, and concluded that ^{18}F-FDG PET has some concordance with the results of bone marrow biopsy for the detection of bone marrow infiltration in the staging of patient with variations among subtypes of lymphoma (22). Hence, the role of ^{18}F-FDG PET needs to be validated in NK/T-cell lymphoma and EBV ISH deemed more sensitive than ^{18}F-FDG PET based on our study.

Based on our data, we postulate that patients with minimal bone marrow involvement may benefit from early intensive treatment with consideration of hematopoietic stem cell transplantation in their treatment strategy. Presently, autologous hematopoietic stem cell transplantation is not recommended outside the context of a clinical trial in stage I/II disease (12). However, several groups, including our group, reported favorable outcome in high-risk patients who received high-dose chemotherapy with autologous hematopoietic stem cell transplantation (20, 23, 24). The Hong Kong group is using plasma EBV DNA level as a stratification factor to identify high-risk patients who might benefit from early autologous hematopoietic stem cell transplantation and currently conducting a prospective study to validate the hypothesis (20). In prospective studies, patients with minimal bone marrow involvement by EBER-1 ISH should be categorized as high risk and the efficacy of high-dose chemotherapy and autologous hematopoietic stem cell transplantation should be tested in this subset of patients. Additionally, the role of involved-field radiotherapy should be clarified in this particular subset of patients.

Considering the fact that 15.4% of the patients with clinically localized NK/T-cell lymphomas showed minimal bone marrow involvement by EBER-1 ISH, bone marrow EBER-1 ISH may be considered during staging evaluation in NK/T-cell lymphoma patients to improve accuracy in staging. Nevertheless, a consensus on the definition of minimal bone marrow involvement and on the most effective method for detecting EBV-positive malignant cells should be further verified among institutions and countries.

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