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Rev. Med. Virol. 2008; **18**: 305–319.
DOI: 10.1002/rmv

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Autologous Hematopoietic Stem Cell Transplantation in Extranodal Natural Killer/T Cell Lymphoma: A Multinational, Multicenter, Matched Controlled Study

Jeeyun Lee,[1] Wing-Yan Au,[2] Min Jae Park,[1] Junji Suzumiya,[3] Shigeo Nakamura,[4] Jun-Ichi Kameoka,[5] Chikara Sakai,[6] Kazuo Oshimi,[7] Yok-Lam Kwong,[2] Raymond Liang,[2] Harry Yiu,[8] Kam-Hung Wong,[8] Hoi-Ching Cheng,[8] Baek-Yeol Ryoo,[9] Cheolwon Suh,[10] Young Hyeh Ko,[11] Kihyun Kim,[1] Jae-Won Lee,[12] Won Seog Kim,[1] Ritsuro Suzuki[13]

Extranodal natural killer (NK)/T cell lymphoma, nasal type, is a recently recognized distinct entity and the most common type of non–B cell extranodal lymphoma in Asia. This retrospective analysis studied the potential survival benefits of hematopoeitic stem cell transplantation (HSCT) compared with a historical control group. A total of 47 patients from 3 previously published series of HSCT were matched according to NK/T cell lymphoma International Prognostic Index (NKIPI) risk groups and disease status at transplantation with 107 patients from a historical control group for analysis. After a median follow-up of 116.5 months, the median survival time was not determined for the HSCT group, but it was 43.5 months for the control group (95% confidence interval [CI] = 6.7 to 80.3 months; $P = .127$, log-rank test). In patients who were in complete remission (CR) at the time of HSCT or at surveillance after remission, disease-specific survival rates were significantly higher in the HSCT group compared with the control group (disease-specific 5-year survival rate, 87.3% for HSCT vs 67.8% for non-HSCT; $P = .027$). In contrast, in subgroup analysis on non-CR patients at the time of HSCT or non-HSCT treatment, disease-specific survival rates were not significantly prolonged in the HSCT group compared with the control group (1-year survival rate, 66.7% for HSCT vs 28.6% for non-HSCT; $P = .141$). The impact of HSCT on the survival of all patients was significantly retained at the multivariate level with a 2.1-fold (95% CI = 1.2- to 3.7-fold) reduced risk of death ($P = .006$). HSCT seems to confer a survival benefit in patients who attained CR on postremission consolidation therapy. These findings suggest that, in particular, patients in CR with high NKIPI risk scores at diagnosis should receive full consideration for HSCT.

Biol Blood Marrow Transplant 14: 1356-1364 (2008) © *2008 American Society for Blood and Marrow Transplantation*

KEY WORDS: NK/T-cell lymphoma, autologous hematopoietic stem cell transplantation, chemotherapy

Extranodal natural killer (NK)/T cell lymphoma, nasal type, is a recently recognized distinct entity in the World Health Organization (WHO) classification of lymphoid tumors [1]. This lymphoma occurs more

From the [1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Medicine, Queen Mary Hospital, Hong Kong; [3]First Department of Internal Medicine, Fukuoka University School of Medicine, Fukuoka, Japan; [4]Department of Pathology, Nagoya University School of Medicine, Nagoya, Japan; [5]Department of Rheumatology and Haematology, Tohoku University School of Medicine, Sendai, Japan; [6]Department of Hematology and Oncology, Chiba Cancer Center, Chiba, Japan; [7]Department of Hematology, Juntendo University, Tokyo, Japan; [8]Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong; [9]Department of Hematology-Oncology, Korea Cancer Center Hospital, Seoul, Korea; [10]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [11]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [12]Department of Statistics, Korea University, Seoul, Korea; and [13]Department of Hematopoietic Stem Cell Transplantation Data Management, Nagoya University School of Medicine, Nagoya, Japan.

J. Lee and W.Y. Au contributed equally as first authors.

The authors have no conflicts of interest to declare.

Financial disclosure: See Acknowledgments on page 1364.

Correspondence and reprint requests: Won Seog Kim, MD, PhD, Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong Kangnam-Gu, Seoul 135-710 Korea (e-mail: wskimsmc@skku.edu) or Ritsuro Suzuki, MD, PhD, Department of Hematopoietic Stem Cell Transplantation Data Management, Nagoya University School of Medicine, 1-1-20 Daiko-Minami, Higashi-Ku, Nagoya 461-0047, Japan (e-mail: r-suzuki@med.nagoya-u.ac.jp).

1083-8791/08/1412-0001$34.00/0
doi:10.1016/j.bbmt.2008.09.014

frequently in Asia than in Western countries and is the most common type of non–B cell extranodal lymphoma in Asia [2]. The treatment outcome for NK/T cell lymphomas depends on disease stage. Overall, long-term survival in these lymphomas, reported as 30% to 40% [3-6], tends to be inferior to that for other aggressive lymphomas. Even in localized NK/T cell lymphomas, primary chemotherapy and/or radiotherapy (RT) results in complete remission (CR) rates of 40% to 60%, with 5-year overall survival (OS) rates of 42% to 83% [3,4,7-11], with high systemic failure rates of 25% to 30% [7-9,12].

In an effort to identify strategies for improving these low success rates in treating NK/T cell lymphoma, the use of high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (HSCT) has been investigated [13-17]. Determining the survival benefit of HSCT based on the results of these studies is difficult, however, because of the small size as well as the heterogeneous nature of the patient cohorts.

Recently, a prognostic model specific for NK/T cell lymphoma (NK/T cell lymphoma International Prognostic Index [NKIPI]) has been proposed and validated [6,18]. Clinical variables included in the NKIPI risk scoring system are B symptoms, stage, lactic dehydrogenase (LDH) level, and regional lymphadenopathies. Owing to its extranodal characteristics, the prognostic impact of the IPI has been controversial in this particular subtype of non-Hodgkin lymphoma (NHL). Similar to other prognostic models, the NKIPI has the major aim of identifying high-risk patients and thereby provide better risk-based stratification for optimal treatment.

To explore the potential benefits of autologous HSCT, we have pooled and reanalyzed data from 3 previously published series [6,13,14]. To critically evaluate the role of autologous HSCT, we compared those results with those for a matched control group identified from historical data.

PATIENTS AND METHODS

Patients and Data Collection

Our cohort comprises 59 patients with NK/T cell lymphomas who underwent autologous HSCT reported in 3 previous studies from Korea, Hong Kong, and Japan [6,13,14]. From these 59 patients, 48 were selected for reanalysis (Korea, n = 16 [6]; Hong Kong, n = 16 [13]; Japan, n = 16 [14]). Patient selection was based on availability from a historical control group of patients who were matched according to NKIPI risk group (risk score 0-1 vs 2-4) and disease status at transplantation (first CR [CR1], second CR [CR2] vs partial remission [PR]/no response [NR]), at a ratio of 1:3. In cases where the NKIPI score was not available at the time of analysis, only disease status was considered for matching criteria. The sources of the matching control group were the lymphoma data registry for each study group. The order of priority in selection criteria for matched control cases was NKIPI risk score, followed by disease status at transplantation or conventional treatment/observation. The matched control cases (n = 107) received conventional chemotherapy with or without RT (n = 34), RT alone (n = 5) as salvage therapy, or observation (n = 68) at CR1 or CR2 as postremission care instead of HDC/autologous HSCT. All patients had pathologically confirmed NK/T cell lymphoma according to the WHO classification [1]. One patient with negative Epstein-Barr virus (EBV) in situ hybridization from the HSCT group was excluded from the final analysis; thus, the group from Japan included 15 patients.

Extranasal NK/T cell lymphoma was defined as described previously [3]. In brief, upper aerodigestive tract NK/T cell lymphoma (UNKTL) was defined as that involving the nasal cavity, nasopharynx, and the upper aerodigestive tract, whereas extra-upper aerodigestive tract NK/T cell lymphoma (EUNKTL) included lymphomas occurring at all other sites [3]. The following clinical data were collected from the medical records: demographic information, LDH level at diagnosis, initial Ann Arbor stage, IPI at diagnosis, NKIPI at diagnosis, presence or absence of B symptoms, performance status, date of diagnosis, date of autologous HSCT, disease status at transplantation, transplantation outcome, salvage treatment type and outcome, date of last follow-up, and cause of death. The study design was approved by the Samsung Medical Center's Institutional Review Board.

Chemotherapy

Each patient received 1 of the following initial treatment modalities: (1) an anthracycline-containing chemotherapeutic regimen with or without RT (n = 125), (2) a non–anthracycline-containing chemotherapeutic regimen with or without RT (n = 15), (3) involved-field RT (IFRT) as the primary treatment (n = 13), or (4) surgery plus RT (n = 1). Anthracycline-based regimens used included CHOP (cyclophosphamide, (Cy) doxorubicin, vincristine, and prednisolone; n = 68), dose-escalated CHOP (deCHOP; n = 1), velCHOP (velcade plus CHOP; n = 1), CEOP (Cy, epirubicin, vincristine, and prednisolone; n = 14), CEOP/ProMACE (CEOP followed by Cy, doxorubicin, etoposide, and prednisone; n = 4), MACOP B (methotrexate [MTX], doxorubicin, Cy, vincristine, prednisone, and bleomycin; n = 2), CHOEP (Cy, doxorubicin, vincristine, etoposide, and prednisolone; n = 6), ProMace (n = 3), ProMace/Cytabom (ProMace plus cytabarabine, bleomycin, vincristine, MTX, and leucovorin; n = 21), COPBLAM (Cy, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine; n = 2), EPOCH (etoposide, doxorubicin, vincristine, Cy, and prednisolone; n = 1),

cisplatin/Cy/adriamycin/vindesine/prednisolone (n = 1), and epi-COP (epirubicin, Cy, vincristine, prednisolone; n = 1). The non–anthracycline-containing regimens used were IMEP (ifosfamide, MTX, and etoposide; n = 3), ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine; n = 1), DHAP (dexamethasone, cytarabine, and cisplatin; n = 1), DeVIC (carboplatin, etoposide, ifosfamide, and dextamethasone; n = 1), IMVP-16 (ifosfamide, MTX, and etoposide; n = 2), and VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone; n = 7). In patients with localized disease, IFRT was given at the physician's discretion after chemotherapy. Treatment response was assessed according to standard response criteria [19].

HDC/Autologous HSCT

The procedures for HDC and autologous HSCT have been described previously [13,14,20]. In brief, the following conditioning regimens were used: CBV (etoposide, carmustine, and Cy; n = 14), BEAM (carmustine, etoposide, cytarabine, and melphalan (Mel); n = 12), MCEC (ranimustine, Cy, etoposide and carboplatin; n = 8), BEAC (carmustine, etoposide, cytarabine, and Cy; n = 2), Cy/TBI (Cy and total body irradiation; n = 2), VCT (etoposide, Cy and TBI; n = 2), and others (n = 7).

Statistical Analysis

Disease-specific survival and relapse-free survival (RFS) were estimated using the Kaplan-Meier method. Disease-specific survival was calculated from the date of diagnosis to the date of death from the disease or the last follow-up. RFS was calculated from the date of CR to the first documented relapse in patients who attained CR. Survival rates were compared for statistical differences using log-rank analysis. Survival rates were compared for statistical differences by using log-rank analysis. Continuous biological variables were dichotomized for log-rank analysis. A backward-stepwise Cox regression analysis was performed to delineate prognostic factors at the multivariate level, and all hazard ratios (HRs) were adjusted for age. P values $< .05$ were considered statistically significant, and all P values correspond to 2-sided significance tests.

RESULTS

Patient Characteristics

A total of 47 patients who underwent autologous HSCT were compared with 107 matched controlled cases. Baseline characteristics are summarized in Table 1. All clinical parameters except age and initial Ann Arbor stage were relatively well balanced between the control group and the study group. The median time from diagnosis to transplantation was 8.8 months (range, 2.1 to 86.3 months). The proportion of patients under age 60 years was significantly higher in the autologous HSCT group compared with the control group (95.7% in the autologous HSCT group vs 72.0% in the control group; $P = .001$). In addition, the proportion of patients with localized disease was lower in the autologous HSCT group (66.0%) than in the non-HSCT group (82.2%) ($P = .038$). Otherwise, there were no significant differences in distributions of sex, performance status, LDH level, IPI risk group, presence of B symptoms, anatomic category, NKIPI risk group, or primary treatment modality between the 2 groups.

Autologous HSCT Outcome

More than 90% of the patients in each group received primary chemotherapy with or without IFRT (Table 1). Approximately 2/3 of the patients received CBV, BEAM, or MCEC as the conditioning regimen before HSCT. Of the HSCT group, 30% (n = 14) were in CR1, 28% (n = 13) were in CR2, 28% (n = 13) were in PR/SD, and 15% (n = 7) were in PD at the time of transplantation. Using an intent-to-treat analysis, 66.0% (n = 31) attained CR after HSCT, 4.3% (n = 2) attained PR, and 19.1% (n = 9) had PD. Four fatal toxicities were observed, with a treatment-related mortality (TRM) rate of 8.5% (septic shock, n = 1; pneumonia, n = 1; unspecified, n = 2). Of the 31 patients who attained CR after HSCT, 13 (41.9%) experienced relapse; the median RFS from the date of CR to the first documented relapse or follow-up was 23.3 months (range, 0.2 to 180.3 months). Of the 13 patients who experienced relapse, 5 received salvage chemotherapy, 4 received RT, 2 underwent allogeneic HSCT, and 2 received palliative treatment. After a median follow-up of 99.8 months post-HSCT (range, 23.4 to 180.9 months), the median survival time after HSCT has not yet been reached. There was no significant difference in survival between the HSCT and control groups (56.2% vs 47.6%; $P = .127$) (Figure 1B).

Prognostic Analysis for Autologous HSCT

The following clinical factors predicted poor survival of patients undergoing autologous HSCT in univariate analysis: advanced Ann Arbor stage (stage III/IV; $P = .045$) and disease status at the time of transplantation (non-CR; $P < .001$) (Table 2). For RFS after autologous HSCT, advanced Ann Arbor stage (stage III/IV; $P = .021$), elevated LDH level ($P = .026$), non-CR at the time of transplantation ($P = .001$), and high IPI risk group (high-intermediate/high; $P = .005$) predicted relapse after HSCT. In multivariate analysis with stage, the presence of B symptoms, anatomic category, and disease status at HSCT, only disease status at HSCT retained its statistical significance for RFS ($P < .001$; HR = 3.5; 95% confidence

Table 1. Patient and Treatment Characteristics

	All Patients	HSCT	Controls	*P* Value
Total cases, n (%)	154 (100)	47 (30.5)	107 (69.5)	
Median age, years (range)	47 (17 to 80)	42 (17 to 62)	52 (17 to 80)	
Age, years, n (%)				
≤ 60	122 (79.2)	45 (95.7)	77 (72.0)	.001
> 60	32 (20.8)	2 (4.3)	30 (28.0)	
Sex, n (%)				
Male	111 (72.1)	34 (72.3)	77 (72.0)	.962
Female	43 (27.9)	13 (27.7)	30 (28.0)	
Performance status, n (%)				
ECOG 0-1	139 (90.3)	43 (91.5)	96 (89.7)	.733
ECOG 2-4	15 (9.7)	4 (8.5)	11 (10.3)	
Ann Arbor stage, n (%)				
Limited (I-II)	118 (77.1)	31 (66.0)	87 (82.2)	.038
Advanced (III-IV)	36 (23.5)	16 (34.0)	20 (17.8)	
LDH (n = 150), n (%)				
≤ Upper limit of normal	77 (51.3)	23 (51.1)	54 (51.4)	.972
> Upper limit of normal	73 (48.7)	22 (48.9)	51 (48.6)	
IPI risk group (n = 151), (%)				
Low/low-intermediate	127 (84.1)	37 (82.2)	90 (84.9)	.680
High-intermediate/high	24 (15.9)	8 (17.8)	16 (15.1)	
B symptoms, n (%)				
Positive	97 (63.0)	27 (57.4)	70 (65.4)	.345
Negative	57 (37.0)	20 (42.6)	37 (34.6)	
Anatomic category, n (%)				
UNKTL	141 (91.6)	42 (89.4)	99 (92.5)	.516
EUNKTL	13 (8.4)	5 (10.6)	8 (7.5)	
NKIPI risk group (n = 145), n (%)				
Low risk (group 1-2)	80 (55.2)	23 (54.8)	57 (55.3)	.949
High risk (group 3-4)	65 (44.8)	19 (45.2)	46 (44.7)	
Primary treatment, n (%)				
Anthracycline-based chemotherapy ± RT	125 (81.2)	41 (87.2)	84 (78.5)	
Non-anthracycline-based chemotherapy ± RT	15 (9.7)	3 (6.4)	12 (11.9)	.600
RT only	13 (8.4)	3 (6.4)	10 (10.2)	
Surgical excision + RT	1 (0.6)	0 (0.0)	1 (0.8)	
Disease status at treatment, n (%)				
CR1	61 (39.6)	14 (29.8)	47 (43.9)	
CR2	34 (22.1)	13 (27.7)	21 (19.6)	.232
PR/NR/PD	59 (38.3)	20 (42.6)	39 (36.4)	

NKIPI indicates natural killer/T cell lymphoma International Prognostic Index; UNKTL, upper aerodigestive NK/T cell lymphoma; EUNKTL, extra-upper aerodigestive NK/T cell lymphoma; RT, radiotherapy; CR1, first complete response; CR2, second complete response; PR, partial response; NR, no response; PD.

interval [CI] = 1.6 to 7.9) and disease-specific survival (P <.001; HR = 7.2; 95% CI = 4.4 to 1.6). Thus, disease status at autologous HSCT was the most important prognostic factor for survival and RFS.

Impact of HSCT on Survival in NK/T Cell Lymphoma

After a median follow-up of 116.5 months (range, 13.2 to 234.0 months), the median survival was 47.3

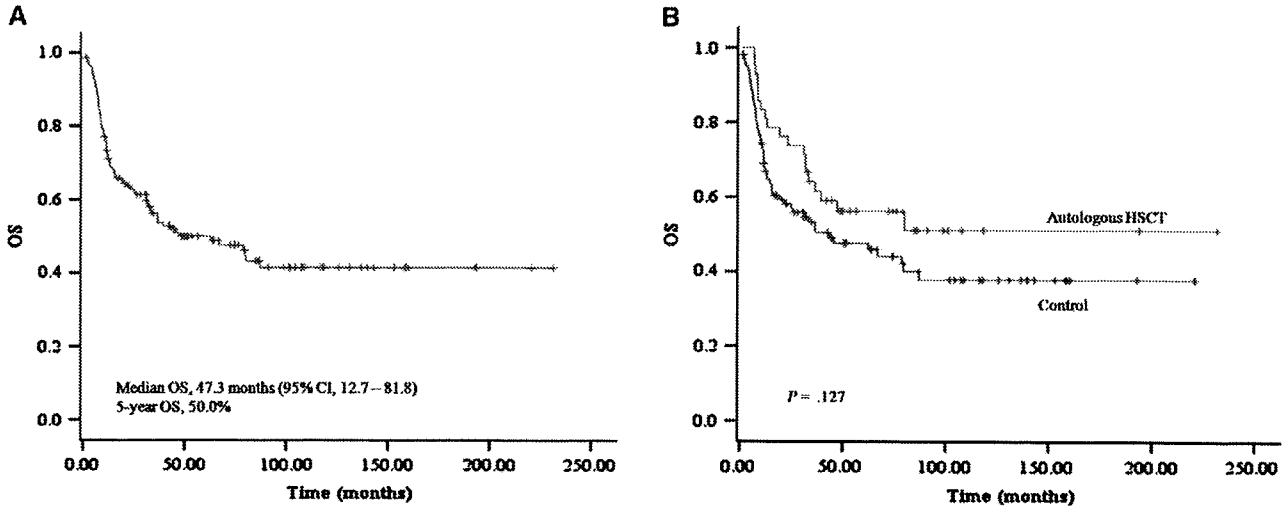

Figure 1. Survival of all patients (A) and survival according to HSCT (B).

Table 2. Univariate Analysis for the Patients with HSCT

Parameters	Relapse-Free Survival		Disease-Specific Survival	
	Median (95% CI), Months	P Value	Median (95% CI), Months	P Value
Age, years				
≤ 60	13.7 (0.0 to 30.8)	.600	NA	NA
> 60	NA			
Ann Arbor stage				
Limited (I/II)	NR	.021	NR	.045
Advanced (III/IV)	4.2 (0.0 to 9.3)		36.5 (11.0 -62.0)	
LDH				
≤ Upper limit of normal	NR	.026	NR	.145
> Upper limit of normal	6.2 (0.0 to 29.8)		31.8 (0.0 to 104.4)	
B symptoms				
Positive	16.8 (0.0 to 44.4)	.654	NR	.536
Negative	19.3 (0.0 to 43.6)		NR	
Anatomic category				
UNKTL	16.8 (0.0 to 34.6)	.527	NR	.152
EUNKTL	2.2 (1.3 to 3.2)		36.5 (0.0 to 73.5)	
Disease status at HSCT				
CR	NR	.001	NR	<.001
Non-CR	2.5 (1.7 to 3.4)		19.2 (0.0 to 56.5)	
IPI risk group				
Low/low-intermediate	21.0	.005	NR	.223
High-intermediate/high	1.8 (1.2 to 2.4)		19.2 (0.0 to 81.0)	
NKIPI risk group				
Low risk (group 1-2)	NR	.086	NR	.066
High risk (group 3-4)	6.2 (0.0 to 20.1)		31.1 (0.0 to 70.7)	

NA indicates not applicable; ; NKIPI indicates natural killer/T cell lymphoma International Prognostic Index; UNKTL, upper aerodigestive NK/T cell lymphoma; EUNKTL, extra-upper aerodigestive NK/T cell lymphoma; RT, radiotherapy; CR, complete response; NR, no response; LDH, lactate dehydrogenase; HSCT, hematopoietic stem cell transplantation.

months (95% CI = 12.7 to 81.8) for all patients (Figure 1A). The median survival time had not yet been reached for the HSCT group, but it was 43.5 months for the control group (95% CI = 6.7 to 80.3 months; P = .127, log-rank test) (Figure 1B). For all patients in both groups, the clinical factors significantly predicting unfavorable survival in univariate analysis were performance status (Eastern Cooperative Oncology Group [ECOG] 2 to 4; P = .042), advanced Ann Arbor stage (stage III/IV; P = .02), elevated LDH level (P = .010), anatomic category (EUNKTL; P = .017), disease status at treatment (non-CR; P < .001), IPI (high-intermediate/high; P = .027), and NKIPI (group 3-4; P = .003) (Table 3).

Clinical parameters included in the multivariate analysis were performance status (0 to 1 vs ≥ 2), Ann Arbor stage (I/II vs III/IV), LDH level (normal vs elevated), anatomic category (UNKTL vs EUNKTL), disease status at treatment (CR1/CR2 vs non-CR), and HSCT versus non-HSCT. A backward-conditional Cox regression model was used. Significant prognostic factors for survival in all patients were LDH level (P = .005; HR = 2.0; 95% CI = 1.2 to 3.2), disease status at treatment (P = < .001; HR = 7.8; 95% CI = 4.6 to 13.0), and HSCT (P = .006; HR = 2.1; 95% CI = 1.2 to 3.7) (Table 4).

Influence of Autologous HSCT on Survival in Subgroup Analyses

We performed subgroup analyses in an attempt to identify patients who would potentially benefit from HSCT. In those patients who were in CR1 or CR2 at the time of HSCT or surveillance after remission, disease-specific survival rates were significantly higher in the HSCT group compared with the control group (disease-specific 5-year survival rate, 87.3% for HSCT vs 67.8% for non-HSCT; P = .027, log-rank test) (Figure 2A). We also performed subgroup analyses according to NK-IPI risk group (low risk vs high risk) (Figure 2B, C). In the low-risk group (group 1-2), there was no significant difference in survival between the HSCT and control groups (disease-specific 5-year survival rate, 86.7% for HSCT [n = 16] vs 69.1% for non-HSCT [n = 38]; P = .291, log-rank test) (Figure 2B). In the high-risk group (group 3-4), however, the HSCT group (n = 6) seemed to have more favorable clinical course compared with the control group (n = 27) in terms of survival with marginal statistical significance (disease-specific 5-year survival rate, 100% vs 51.2%; P = .053, log-rank test) (Figure 2C). For those patients who were in PR at the time of HSCT or other treatment, there was no difference in survival between the HSCT group and the control group (disease-specific 5-year survival rate, 29.6% vs 22.2%; P = .472, log-rank test) (data not shown).

Subgroup analyses on non-CR patients at the time of HSCT or non-HSCT treatment (chemotherapy with or without RT or RT alone) revealed no significant difference in disease-specific survival rates between the HSCT and control groups (1-year survival rate, 66.7% vs 28.6%; P = .141, log-rank test) (Figure 3A). Further subgroup analyses demonstrated

Table 3. Univariate Analyses for Disease-Specific Survival of All Patients

Parameter	Median (95% CI), Months	*P* Value
Age, years		
≤ 60	62.4 (22.6 to 102.2)	.901
> 60	33.5 (19.5 to 42.4)	
Performance status		
ECOG 0-1	66.8 (7.4 to 87.2)	.042
ECOG 2-4	36.5 (0.0 to 77.2)	
Ann Arbor stage		
Limited (I/II)	NR	.002
Advanced (III/IV)	25.0 (3.2 to 46.9)	
LDH		
≤ Upper limit of normal	NR	.010
> Upper limit of normal	31.1 (6.6 to 55.5)	
B symptoms		
Positive	36.7 (0.0 to 78.1)	.631
Negative	66.8 (21.1 to 112.6)	
Anatomic category		
UNKTL	78.8 (42.1 to 115.4)	.017
EUNKTL	19.2 (10.1 to 28.4)	
HSCT		
Yes	NR	.127
No	43.5 (6.7 to 80.3)	
Disease status at HSCT or chemotherapy		
CR	NR	<.001
Non-CR	10.8 (8.0 to 13.7)	
IPI risk group		
Low/low-intermediate	79.6 (20.2 to 104.6)	.027
High-intermediate/high	25.0 (0.2 to 49.9)	
NKIPI risk group		
Low risk (group 1-2)	NR	.003
High risk (group 3-4)	30.9 (10.5 to 51.3)	

NA indicates not applicable; NKIPI indicates natural killer/T cell lymphoma International Prognostic Index; UNKTL, upper aerodigestive NK/T cell lymphoma; EUNKTL, extra-upper aerodigestive NK/T cell lymphoma; RT, radiotherapy; CR, complete response; NR, no response; LDH, lactate dehydrogenase; HSCT, hematopoietic stem cell transplantation.

Table 4. Multivariate Analysis for Disease-Specific Survival of All Patients

Parameters	Relative Risk	95% CI	*P* value
Performance status: ECOG 0-1 versus 2-4	0.6	0.3 to 1.4	.233
Ann Arbor stage: I/II versus III/IV	1.6	0.9 to 2.8	.129
LDH: ≤ Upper limit of normal versus > upper limit of normal	2.0	1.2 to 3.2	.005
Anatomic category: UNKTL versus EUNKTL	1.4	0.6 to 3.0	.457
Disease status at HSCT or chemotherapy: CR versus non-CR	7.8	4.6 to 13.0	<.001
HSCT: Yes versus no	2.1	1.2 to 3.7	.006

NA indicates not applicable; NKIPI indicates natural killer/T cell lymphoma International Prognostic Index; UNKTL, upper aerodigestive NK/T cell lymphoma; EUNKTL, extra-upper aerodigestive NK/T cell lymphoma; RT, radiotherapy; CR, complete response; NR, no response; LDH, lactate dehydrogenase; HSCT, hematopoietic stem cell transplantation.

no notable survival difference between the 2 groups in non-CR patients when subcategorized into low-risk and high-risk NK-IPI groups (Figures 3B and C).

DISCUSSION

This study represents the first multinational collaborative study exploring the role of HDC and HSCT in the treatment of patients with NK/T cell lymphomas. Although HSCT to treat other types of lymphomas (especially diffuse large B cell lymphoma) has been studied extensively, the definite role of and specific indications for HSCT in treating NK/T cell lymphomas have not yet been systematically established. We and few other groups have previously reported poor survival outcome in patients with NK/T cell lymphomas [3-6]. Although several studies have investigated the role of HSCT in treating NK/T cell lymphomas [13-17], they could not conclusively demonstrate the survival benefit from HSCT due to a small number of patients and the lack of a control arm. To overcome these obstacles, we undertook a multinational, multicenter matched control study to determine the potential survival benefit of HSCT in treating NK/T cell lymphomas, as well as to identify subgroups of patients who might benefit the most from HSCT.

Our data reveal several interesting findings. There was a trend toward better survival in the HSCT patients compared with the historical control group, although the difference was not statistically significant (disease-specific 5-year survival rate, 56.2% for HSCT vs 47.6% for non-HSCT; $P = .127$). The impact of HSCT on survival was significantly retained at multivariate level, with a 2.1-fold (95% CI = 1.2 to 3.7) reduced risk of death ($P = .006$). The most important prognostic factor influencing RFS and survival after HSCT was disease status at the time of transplantation ($P < .001$) (Table 2). Patients who did not attain CR at the time of transplantation had a 7.2-fold (95% CI = 4.4 to 11.6) greater risk of death compared with those who were in CR (data not shown).

Furthermore, disease-specific survival was significantly better in patients in CR in the HSCT group compared with those in the control group (disease-specific 5-year survival rate, 87.3% vs 67.8%; $P = .027$). The report of the International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas recommended front-line HSCT only in patients who achieve CR [21]. In particular, the patients with high NKIPI demonstrated notably improved survival after undergoing HSCT (Figure 2C), although the small number of cases in this subgroup limited the statistical power ($P = .053$). These patients need longer follow-up to allow any conclusions to be drawn on the statistical significance in survival difference. Based on our findings, we suggest that HSCT should be carefully considered for postremission consolidation therapy in patients with NK/T cell lymphomas, especially those with high NKIPI risk scores.

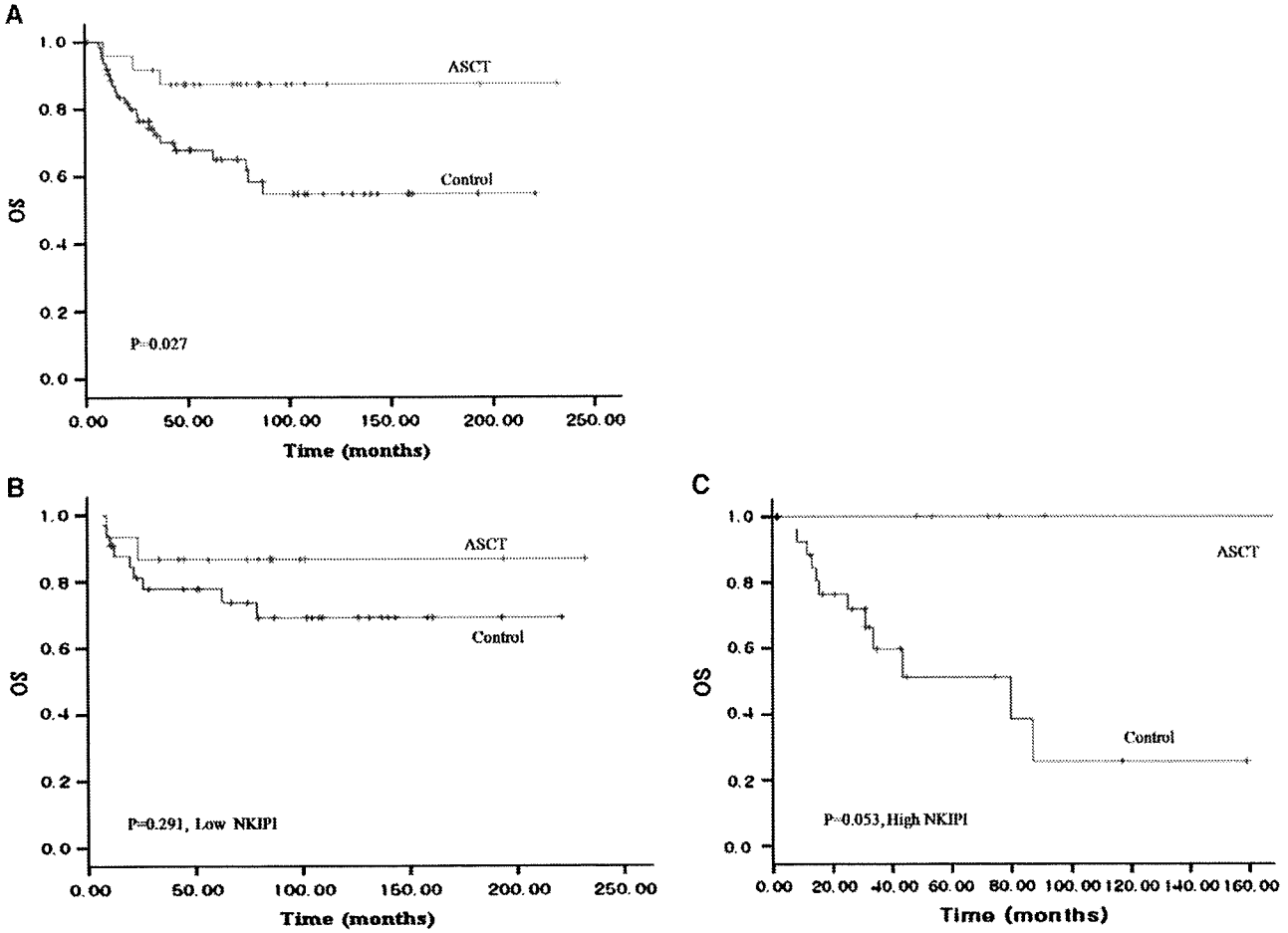

Figure 2. A) OS according to HSCT in CR patients, B) Impact of HSCT on survival of the low NKIPI group (CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

In contrast, subgroup analyses on non-CR patients at the time of HSCT or non-HSCT treatment found that disease-specific survival rates were not significantly prolonged in the HSCT group compared with the control group (1-year survival rate, 66.7% vs 28.6%; $P = .141$ [Figure 3A]. This finding is in agreement with previous studies that found negative outcomes of transplantation in a refractory disease state [20,22-24]. The segregation of patients based on NKIPI was not statistically significant in non-CR patients, although a trend toward better survival was seen in those patients with higher NKIPI who underwent autologous HSCT ($P = .064$; Figure 3C). Whether or not HSCT should be considered in patients with refractory NK/T cell lymphomas, especially those with high NKIPI scores, remains to be determined. Our findings do suggest that patients with refractory NK/T cell lymphomas should be offered therapy with investigational agents or reduced-intensity allogeneic HSCT in the context of clinical trials.

Although HDC/HSCT seemed to confer a survival advantage in our patients with NK/T cell lymphomas, especially those in the high-risk NKIPI group, only 66% of the patients receiving HDC/HSCT achieved CR, of whom 41.9% (n = 12) eventually experienced relapse. In addition, the role of HDC/HSCT was not definite in the patients with PR (disease-specific 5-year survival rate, 29.6% HSCT vs 22.2% for non-HSCT; $P = .472$). A possible explanation for the low CR rate and high relapse rate may be the inefficiency of the conditioning regimens used. Analyzing the efficacy of the conditioning regimen in this study is difficult because of the heterogeneity of the treatment protocols used. Nevertheless, most of the patients received a Cy-based conditioning regimen, which could be a target for a multidrug-resistance gene. Allogeneic HSCT possibly can have a graft-versus-lymphoma effect and reduce relapse rate at the expense of high TRM [25,26]. Another possible strategy to improve the treatment outcome of HDC/HSCT may be to perform transplantation before chemotherapy resistance is allowed to progress, such as when the patient is in CR1 [27]. Consequently, more multinational prospective studies incorporating novel therapies

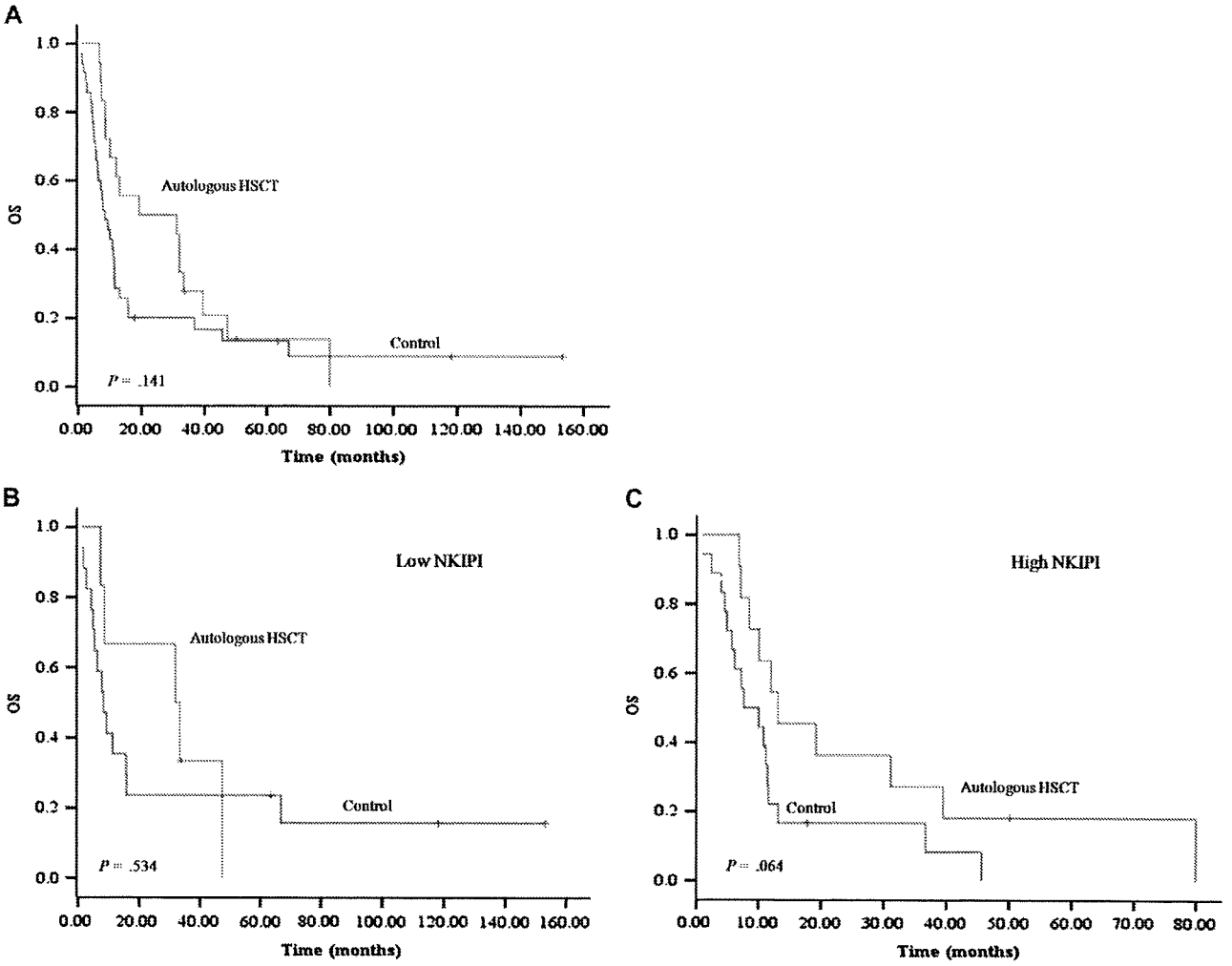

Figure 3. A) OS according to HSCT in non-CR patients, B) Impact of HSCT on survival of the low NKIPI group (non-CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

should be undertaken to improve survival in these patients.

Despite the adoption of a matched control design to minimize potential biases, our study is still limited by the retrospective nature of the analyses. To reduce bias, we matched 2 known prognostic factors known to influence survival in NK/T cell lymphomas: disease status at time of transplantation and NKIPI. Previous studies have confirmed the attainment of CR at the time of transplantation as one of the most powerful prognostic factors for survival after HSCT [15,19,20,23,28]. Thus, we selected a 1:3 ratio of HSCT patients to control patients who did not undergo HSCT as postremission consolidation therapy, but had surveillance alone. For the patients who did not achieve CR at the time of HSCT, we attempted to select control patients who received conventional therapy from the database. There are potential selection biases in the historical control group. The patients in the control group did not undergo HSCT mainly due to different practice guidelines among the institutions in the 3 different nations and differences in patient age. Moreover, the proportion of patients with non-CR (PR/SD/PD) was higher in the HSCT group, likely reflecting current treatment practices. But the clinical variables, including performance status, LDH level, IPI, presence of B symptoms, anatomic category, NK-IPI, disease status, and primary treatment modalities, were well balanced between the 2 arms. There were greater proportions of patients under age 60 years, but the prognostic impact of this was not significant at the univariate level (Table 2), which coincides with results from the Japanese and Korean series [6,14,29]. Another weakness of the present study lies in the heterogeneity of the treatment modalities and HSCT protocols owing to retrospective data collection from 3 different databases from different institutions and different nations.

In summary, collectively, our data indicate that HSCT seemed to confer a survival benefit in patients who attained CR as postremission consolidation therapy. These findings suggest that, in particular, patients

with high NKIPI risk scores (group 3-4) at diagnosis who attain CR should receive full consideration for autologous HSCT.

ACKNOWLEDGMENTS

Financial disclosure: This study was supported by Samsung Medical Center grant OTX1070211.

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NK細胞腫瘍の
患者さんとご家族へ

この小冊子は厚生労働科学研究費補助金（がん臨床研究事業）
「NK細胞腫瘍に対する東アジア多国間治療研究」
（研究代表者：鈴木律朗・名古屋大学）により作成されたものです

ごあいさつ

この小冊子はNK（エヌケー）細胞腫瘍（NK細胞リンパ腫、NK/T細胞リンパ腫など）といわれた患者さんのために作成しました。“悪性リンパ腫”もどのような病気か分からないのに、さらに難しい話をされてとまどっていらっしゃるかもしれません。
そのような“あなた”のために少しでもお役に立つことを目的にこの小冊子をご用意しました。この小冊子が少しでも“あなた”のお役に立つことを願っております。

目次

NK(エヌケー)細胞腫瘍といわれたときに

1) 主治医の先生に以下の点をご確認ください。

①どんなNK細胞腫瘍ですか？ （後にその説明があります 5ページ）

②病期（びょうき）は （後にその説明があります 11ページ）

一般的に“がん”の治療は手術、放射線治療、化学療法（抗がん剤）のいずれかを選んで、あるいは組み合わせて治療を行いますが、NK細胞腫瘍では化学療法と放射線治療を行います。治療方法は、①病型（病気の種類）②病期（病気の広がり）と③患者さんの状態によって決められます。最もよい治療をお受けになるためにこれらの情報がとても重要なので、これらがわかるような検査が必要になります。

2) 次に主治医の先生に検査や治療の大まかなスケジュールをお尋ねください。

ご自身の病気のことや検査、治療の予定が分かると、不安なお気持ちが少しでも和らぐのではないかと思います。この小冊子をご覧になり、ご自身の病気のことを理解されたうえで、治療に臨まれてください。

3) NK細胞腫瘍は稀な腫瘍ですので、詳しく分かっていない事もたくさんあります。

NK細胞腫瘍は、「慢性NK細胞増多症」以外はすべて進行の速い腫瘍ですので、診断確定後は必要な検査をすませて、なるべく早くに治療を開始することが大切です。

NK細胞腫瘍とはどんな病気でしょうか?

――血液細胞のひとつであるNK細胞が
腫瘍(がん)化したものです。

NK細胞腫瘍とは、NK細胞(補足説明1)の“がん”の総称です。つまりNK細胞リンパ腫とNK細胞白血病とを合わせた呼び名です。“がん”になったNK細胞が腫瘤(しゅりゅう:こぶのこと)をつくるとNK細胞リンパ腫と呼び、血液のなかで増えるとNK細胞白血病と呼びます。NK細胞リンパ腫は悪性リンパ腫(以後リンパ腫と呼びます)の一つです。NK細胞リンパ腫もNK細胞白血病も珍しい“がん”のひとつですが、NK細胞リンパ腫は日本や韓国などの東アジアに多いという特徴があります。

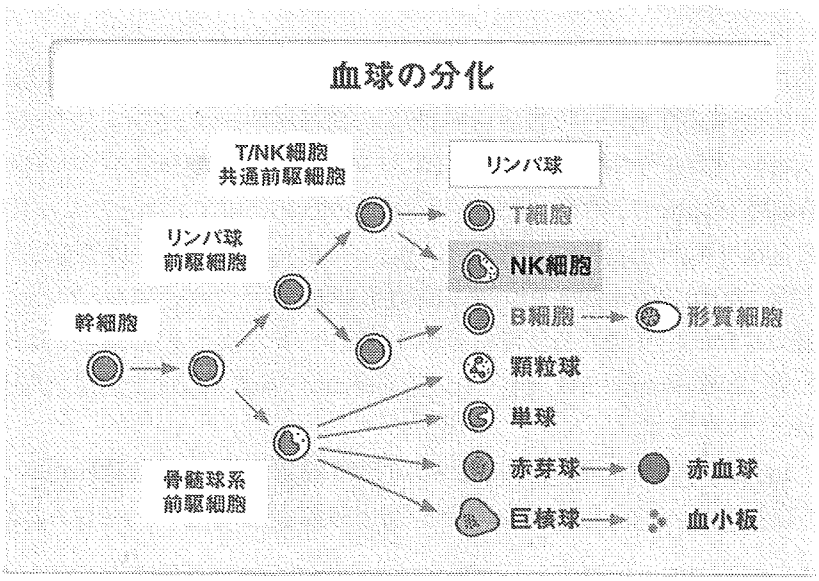
血液の中には酸素を運ぶ赤血球、出血を止める際に重要な働きをする血小板、からだを細菌などから守る白血球の3種類の血球があります。さらに、白血球は大きく5種類に分かれます《図1》。その一つにリンパ球があります。リンパ球はB細胞、T細胞と、T細胞に近いNK細胞というのがあります。これらのリンパ球には様々な分化段階(人間でいえば赤ちゃんが大人になるまでの発達段階と同じようなもの)があり、それぞれの段階のリンパ球が“がん”になってリンパ腫になります。そのため非常に多くの種類のリンパ腫があり、現在では約50種類くらいに分けられ、それぞれに名前がついています。これを病型(びょうけい)といいます。
これらのリンパ球は身体を守る働き方(免疫機能といいます)が違います。B細胞は抗体(こうたい:身体を守るミサイルのようなものです)を作るのに

対して、T細胞はB細胞が抗体を作るのを調整したり、がん細胞やウイルス感染細胞を直接やっつける殺し屋細胞（キラーリンパ球、キラー細胞）となります。NK細胞はT細胞と共通の未熟な細胞（同じ先祖）からできており、殺し屋T細胞に似た働きでがん細胞やウイルス感染細胞を直接やっつけて、身体を守る働きをします。このNK細胞が“がん”になったものをNK細胞腫瘍と呼びます。

補足説明1：

NK細胞はNatural killer(ナチュラルキラー)細胞のNaturalの“N”とkillerの“K”の頭文字をとった略語です。NK細胞腫瘍はNK/T（エヌケー/ティ）細胞腫瘍ともよばれることがあります。

〈図1〉

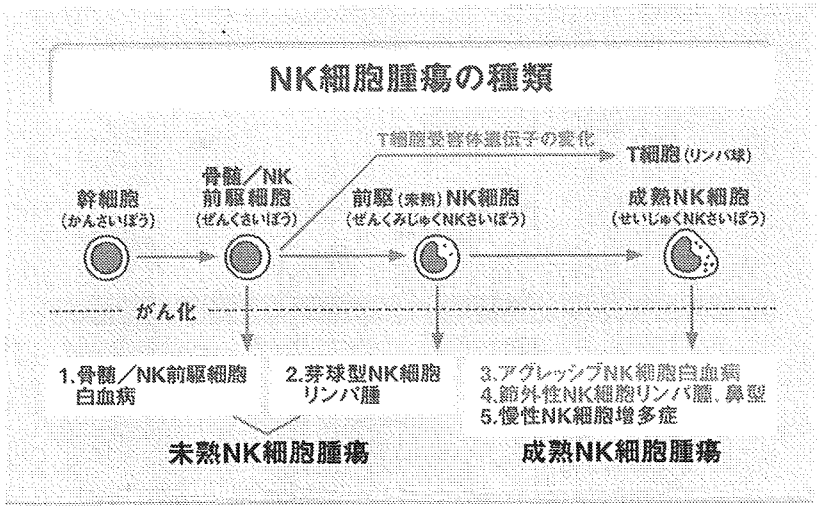


NK細胞腫瘍には どのような種類があるのですか？

――未熟なNK細胞の腫瘍と成熟したNK細胞の腫瘍があります。

ほかの種類の白血球と同じように、NK細胞も未熟な細胞（“芽球:がきゅう”とも呼ばれます）からだんだん分化して（成熟して）、機能をもった成熟NK細胞になります。人間の成長と同じで、赤ちゃんから小児期、青年期になり、社会にでて働くようになるのと同じようなことをイメージしていただければよいと思います。NK細胞腫瘍は未熟な細胞が腫瘍になったものと、成熟したNK細胞が腫瘍になったものに大別されます《図2》。以下に、それぞれの病気についてご説明します。

〈図2〉



未熟なNK細胞腫瘍（みじゅくなNKさいぼうしゅよう）

1. 骨髄／NK前駆細胞白血病（こつずい／NKぜんくさいぼうはっけつびょう）

患者さんは大変少ない病気です。急性骨髄性白血病と同様の治療がされます。

2. 芽球型NK細胞白血病・リンパ腫（がきゅうがたNKさいぼうはっけつびょう・りんぱしゅ）

患者さんは大変少ない病気です。急性白血病と同様の治療がされます。詳しいことはまだわかっていませんが、一部は芽球型形質細胞様樹状細胞腫瘍（がきゅうがたけいしつさいぼうようじゅじょうさいぼうしゅよう）（補足説明2）であることが最近明らかにされました。この腫瘍も珍しい腫瘍で最良の治療法ははっきりしていませんが、急性白血病と同様の治療をされることが多いです。