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.

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

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.

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.

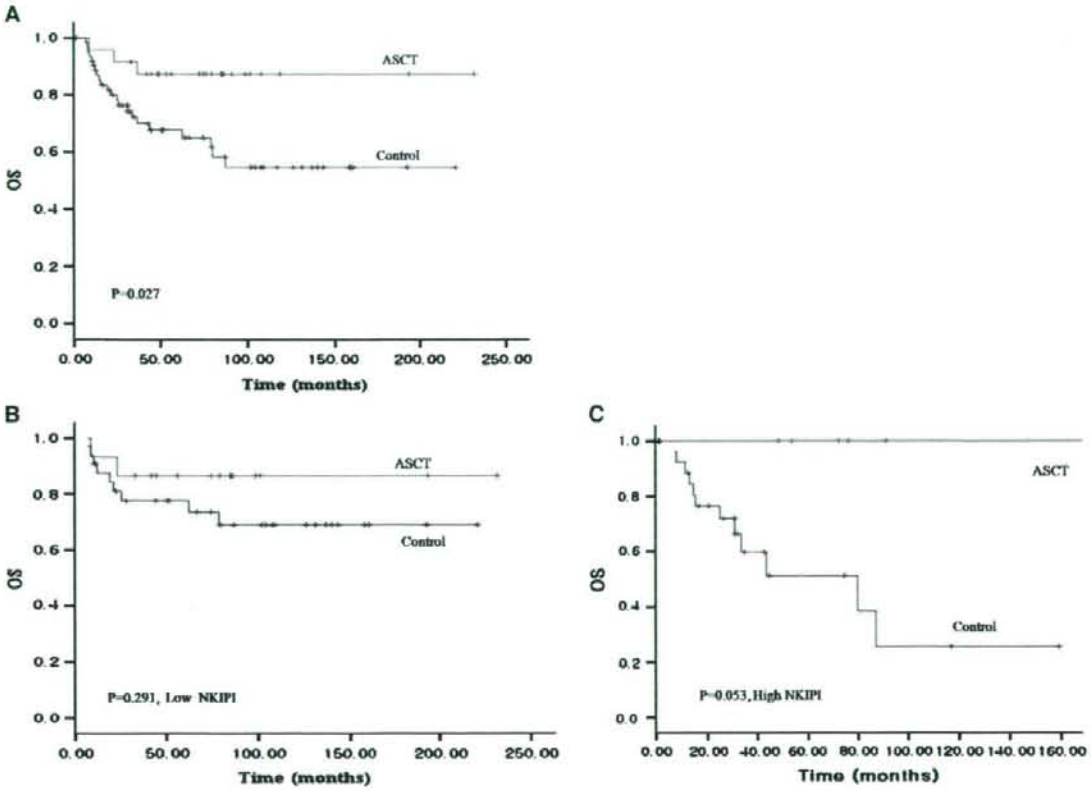

Figure 2. A) OS according to HSCT in CR patients, B) Impact of HSCT on survival of the low NKIPI group (CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

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

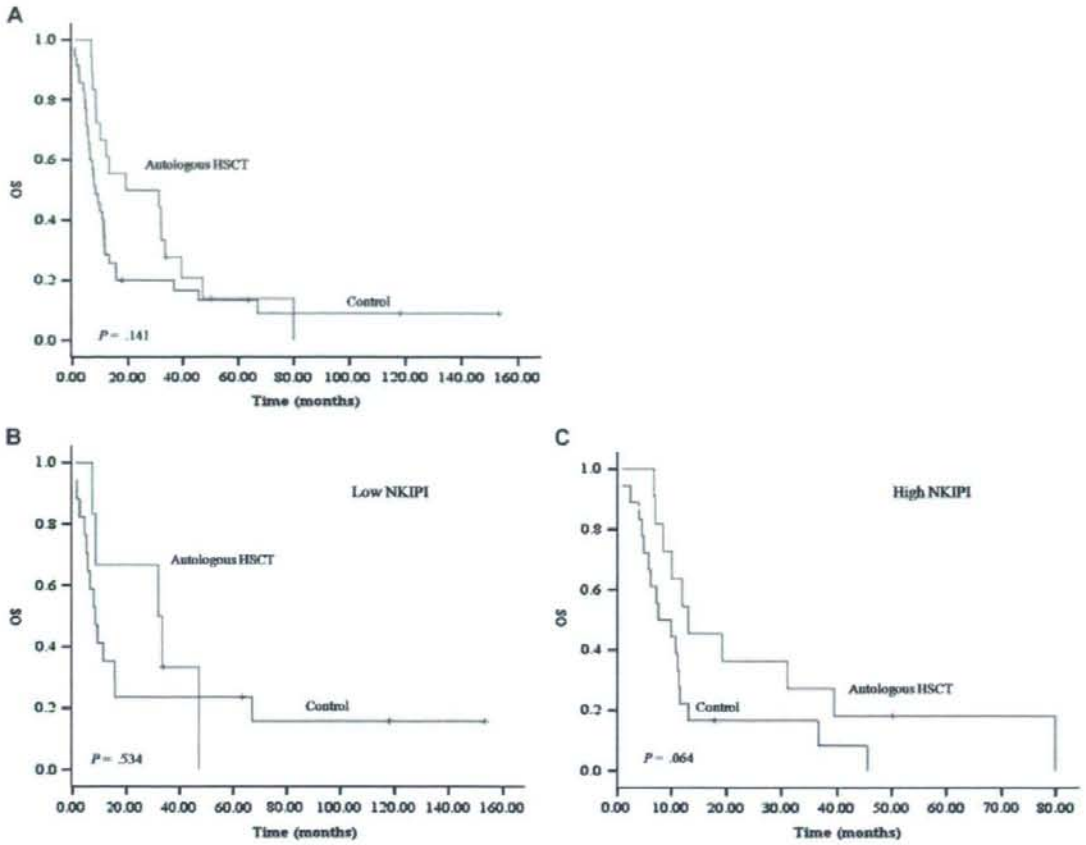

Figure 3. A) OS according to HSCT in non-CR patients, B) Impact of HSCT on survival of the low NKIPI group (non-CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

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.

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