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Older patients with LBCL show comparable outcomes to younger patients and product-specific profiles in CAR-T therapy

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Key Points

- CAR-T therapy shows comparable survival outcomes in older and younger patients with LBCL.
- In younger patients, axi-cel and liso-cel improve PFS vs tisa-cel; in older patients, axi-cel increases nonrelapse mortality vs tisa-cel.

Anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a key treatment option for patients with relapsed or refractory large B-cell lymphoma (LBCL). However, data on its effectiveness and safety in older populations remain limited, particularly in real-world clinical practice. Moreover, comparative outcomes among different CAR-T products across age groups have not yet been fully characterized. We conducted a nationwide retrospective cohort study using data from the Japanese Society for Transplantation and Cellular Therapy. A total of 908 patients who received CAR-T therapy between January 2019 and September 2024 were included. Patients were categorized as younger (aged <65 years) or older (aged ≥65 years). Subgroup analyses were performed by CAR-T product (tisagenlecleucel [tisa-cel], lisocabtagene maraleucel [liso-cel], and axicabtagene ciloleucel [axi-cel]). In univariate analysis, 1-year overall survival (OS) and progression-free survival (PFS) were comparable between younger and older patients (OS, 69.4% vs 65.7% [P = .40]; PFS, 47.9% vs 54.1% [P = .17]). In multivariate analysis, age ≥65 years showed no significant association with OS (hazard ratio, 0.88; 95% confidence interval, 0.65-1.21; P = .44). The incidence of immune effector cell–associated neurotoxicity syndrome was significantly higher in older patients (12.7% vs 7.0%; P = .005). Compared with tisa-cel, axi-cel and liso-cel were associated with superior PFS, predominantly in younger patients. Among older patients, axi-cel was associated with higher nonrelapse mortality rate than tisa-cel. CAR-T therapy is feasible and effective for older patients with LBCL. These findings support age-adapted treatment strategies that consider both the efficacy and toxicity of each product.

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The data of this study are not publicly available due to ethical restrictions, because they exceed the scope of the recipients' and donors' consent for research use in the registry.

The full-text version of this article contains a data supplement.

Introduction

The advent of chimeric antigen receptor T-cell (CAR-T) therapy has marked a significant breakthrough in the treatment of hematologic malignancies. Clinical trials have shown that anti-CD19 CAR-T therapy is highly effective for relapsed/refractory B-cell lymphoma, providing new hope to many patients.[1-3]

The incidence of non-Hodgkin lymphoma increases with age,[4] and B-cell lymphoma, including diffuse large B-cell lymphoma (LBCL), is more commonly diagnosed in older individuals. Age is a critical component of prognostic indices, such as the International Prognostic Index, which is widely used to predict outcomes in patients with aggressive non-Hodgkin lymphoma.[5,6] In autologous/allogeneic hematopoietic stem cell transplantation, a widely used cellular therapy, advanced age is associated with worse outcomes.[7-9] However, the prognostic impact of age in CAR-T therapy remains unclear.

Because older patients are often at increased risk in other treatments, it is essential to thoroughly understand the safety and efficacy of CAR-T therapy in this population. Additionally, CAR-T therapy may cause specific adverse events, including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS),[10-12] the severity of which may range from mild to life-threatening. Therefore, accurate risk assessment and toxicity monitoring are essential when considering CAR-T therapy for older individuals. In Japan, there are no strict age-based restrictions on the administration of CAR-T therapy. Given the nation's rapidly aging population and the increasing incidence of relapsed or refractory B-cell malignancies in older individuals, it is particularly important to evaluate age-associated risks and treatment responses.

Comprehensive assessments of the safety and efficacy of CAR-T therapy in older patients are essential for optimizing clinical outcomes and guiding evidence-based treatment decisions for older patients. Therefore, we conducted a large nationwide study to retrospectively compare the outcomes of older and younger patients with LBCL using the Japanese Cellular Therapy Registry database.

Methods

This retrospective cohort study was conducted using data from the Japanese Society for Transplantation and Cellular Therapy (JSTCT) registry and the Japanese Data Center for Hematopoietic Cell Transplantation. The study was designed by the Cellular Therapy Working Group of the JSTCT and approved by the institutional review board of Kyoto University and the data management committee of the JSTCT. Informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki.

Patients with LBCL who received anti-CD19 CAR-T therapy in Japan between January 2019 and September 2024 were eligible for inclusion. Of the patients registered in the JSTCT database, 908 had complete information on age and survival outcomes and were included in the analysis. Patients were stratified by age into 2 primary groups: those aged <65 years (younger group) and those aged ≥65 years (older group).

Subgroup analyses were conducted within the older cohort (aged ≥65 years), stratified into age groups of 65 to 69, 70 to 74, and ≥75 years. Subgroup analyses were also conducted by CAR-T products, including tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), and axicabtagene ciloleucel (axi-cel), to examine product-specific differences in efficacy and toxicity across age groups.

Tisa-cel was the first CAR-T therapy approved for the treatment of diffuse LBCL in Japan in 2019. Since its approval, tisa-cel has continued to be used in clinical practice and remains a viable therapeutic option. Therefore, in this study, tisa-cel was included as a representative CAR-T product to reflect the current landscape of CAR-T therapy in Japan.

Median follow-up time was estimated by reverse Kaplan-Meier method.

Overall survival (OS) was defined as the time from CAR-T therapy to death or the last date of follow-up. Progression-free survival (PFS) was defined as the time from CAR-T therapy to death, progression, or the last date of follow-up. Progression was defined as the first documentation of progressive or relapsed lymphoma based on clinical, hematologic, radiologic, cytogenetic, or molecular assessments. CRS and ICANS were diagnosed and graded according to the guidelines of the American Society for Transplantation and Cellular Therapy.[12]

Categorical variables were analyzed using the Fisher exact test or the χ^2 test, and continuous variables were compared using the Student *t* test for 2-group comparisons and 1-way analysis of variance for comparisons among 3 groups.

The probabilities of OS and PFS were estimated using the Kaplan-Meier method and compared among groups with the log-rank test. The probabilities of progression and nonrelapse mortality (NRM) were estimated using the cumulative incidence curve[13] and compared using Gray test, considering death without progression as a competing event for progression and progression as a competing event for NRM.[14] If a significant difference was detected in the 3-group comparison, pairwise comparisons were subsequently performed, with *P* values adjusted for multiple testing using the Bonferroni method.

Multivariate analyses of OS and PFS were performed using the Cox proportional hazards model. The following covariates were considered: patient age, serum lactate dehydrogenase (LDH) level measured before lymphodepletion, preinfusion extranodal site, Karnofsky performance status (KPS), disease status at CAR-T therapy, history of autologous stem cell transplantation (ASCT), CAR-T product, and number of previous lines. Multivariate analysis for the incidence of ICANS was performed using a logistic regression model. Covariates included patient age, serum LDH level measured before lymphodepletion, KPS, disease status at CAR-T therapy, and CAR-T product.

All time-to-event outcomes (OS, PFS, progression, and NRM) were measured from the date of CAR-T infusion. All *P* values were 2-sided, and a *P* value <.05 was considered to indicate a significant difference. All calculations were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R.[15] Graph generation was conducted using the survminer package (version 0.4.9).

Results

Patient characteristics

A total of 908 patients were included in the analysis, including 529 aged <65 years (range, 18-64) and 379 aged ≥65 years (range, 65-82). Most patients in the overall cohort received tisa-cel, followed by liso-cel and axi-cel. Performance status (PS) significantly differed between groups, with a lower percentage of older patients having KPS of 90 to 100 ($P = .009$). Prior ASCT was significantly more common in the younger group ($P < .001$). Patients aged ≥65 years were also more likely to have received fewer previous lines of therapy, with 24.0% having ≤2 lines compared to 15.7% in the younger group ($P = .002$). Serum LDH levels, disease status, and extranodal involvement did not significantly differ between the groups. Conditioning regimens were similar between groups, with nearly 90% of all patients receiving fludarabine/cyclophosphamide. Detailed baseline characteristics are summarized in Table 1.

The overall median follow-up time was 12.0 months (95% confidence interval [CI], 11.1-12.0). Follow-up duration was comparable between the younger and older groups: 12.0 months (95% CI, 11.5-12.2) vs 11.9 months (95% CI, 6.7-12.0), with no statistically significant difference ($P = .19$).

Based on the hematopoietic cell transplantation–specific comorbidity index,[16] older patients had significantly higher comorbidity scores. Cardiac arrhythmias, cerebrovascular disease, and prior malignancy were more common in the ≥65-year group (supplemental Table 1). Further analyses stratifying older patients into subgroups (aged 65-69, 70-74, and ≥75 years) are provided in supplemental Table 2.

Efficacy and outcomes

One-year OS rates were 69.4% (95% CI, 64.3-73.9) in the younger group and 65.7% (95% CI, 59.4-71.2) in the older group ($P = .40$; Figure 1A). Similarly, 1-year PFS rates were 47.9% (95% CI, 42.6-52.9) in the younger group and 54.1% (95% CI, 47.9-59.9) in the older group ($P = .17$; Figure 1B). To address potential bias due to very short follow-up, we conducted a sensitivity analysis excluding patients censored within 30 days. The OS and PFS results remained essentially unchanged (supplemental Figure 1), supporting the robustness of the main findings.

The 1-year cumulative incidence of progression was 47.8% (95% CI, 42.7-52.8) in the younger group and 37.6% (95% CI, 32.0-43.3) in the older group ($P = .013$). In contrast, the 1-year cumulative incidence of NRM was 4.3% (95% CI, 2.5-6.8) in the younger group and 8.2% (95% CI, 5.3-12.0) in the older group ($P = .011$; supplemental Figure 2).

In the multivariate Cox regression analysis (Table 2) of the entire cohort, age ≥65 years was not significantly associated with OS (hazard ratio [HR], 0.88; 95% CI, 0.65-1.21; $P = .44$) but was significantly associated with PFS (HR, 0.73; 95% CI, 0.57-0.95; $P = .019$). In contrast, a KPS score of ≤80 was strongly associated with worse outcomes for both OS (HR, 3.66; 95% CI, 2.61-5.13; $P < .001$) and PFS (HR, 2.18; 95% CI, 1.62-2.93; $P < .001$). LDH elevation, extranodal involvement, noncomplete response disease status at CAR-T therapy, and a history of ASCT were also independently associated with both OS and PFS in the multivariate analysis. Compared with tisa-cel, liso-cel was significantly associated with improved OS (0.56; 95% CI, 0.36-0.87; $P = .010$), and both liso-cel and axi-cel were significantly associated with improved PFS (liso-cel [HR, 0.56; 95% CI, 0.34-0.93; $P = .024$]; axi-cel [HR, 0.45; 95% CI, 0.31-0.65; $P < .001$]; Table 2).

Among the older group, we conducted a subgroup analysis stratified by age (ages 65-69, 70-74, and ≥75 years). One-year OS rates were 66.7% (95% CI, 58.2-73.8) in the 65- to 69-year group, 64.7% (95% CI, 53.5-73.9) in the 70- to 74-year group, and 62.1% (95% CI, 39.2-78.4) in the ≥75-year group. No significant differences were observed among these groups ($P = .93$; Figure 1C). Similarly, 1-year PFS rates were 55.4% (95% CI, 46.9-63.0) in the 65- to 69-year group, 54.6% (95% CI, 43.9-64.0) in the 70- to 74-year group, and 42.5% (95% CI, 22.0-61.6) in the ≥75-year group, with no significant differences ($P = .97$; Figure 1D).

Adverse events

The incidence of CRS was similar between younger (aged <65 years) and older group (aged ≥65 years; 75.8% vs 75.2%, $P = .88$). Additionally, no significant difference was observed in the incidence of severe CRS (grade ≥3), which was observed in 13.0% of younger patients and 15.3% of older patients ($P = .33$).

However, the incidence of ICANS was significantly higher in older patients than in younger patients (12.7% vs 7.0%; $P = .005$). Furthermore, the incidence of severe ICANS (grade ≥3) was significantly higher in older patients (6.0% vs 2.9%; $P = .027$; Table 3), with detailed grade distributions provided in supplemental Table 3. Consistent with these findings, multivariate analysis also demonstrated that older patients had a significantly higher risk of developing ICANS after adjustment for baseline characteristics (supplemental Table 4).

Treatment outcomes by CAR-T products

We analyzed treatment outcomes by CAR-T products (tisa-cel, liso-cel, and axi-cel) across younger (aged <65 years) and older groups (aged ≥65 years). Baseline patient characteristics for each age group are summarized in supplemental Tables 5 and 6.

In both the younger and older cohorts, disease status at the time of CAR-T infusion did not significantly differ among the 3 CAR-T products. However, the number of prior lines of therapy was significantly lower for patients receiving axi-cel in both age groups after Bonferroni correction for multiple comparisons.

In both the younger and older cohorts, OS did not differ among the 3 CAR-T products (supplemental Figure 3). In younger patients, PFS differed significantly among CAR-T products ($P < .001$; Figure 2A). Pairwise analyses showed that both axi-cel and liso-cel were associated with significantly better PFS than tisa-cel (adjusted $P = .006$ and .008, respectively), whereas no significant difference was observed between axi-cel and liso-cel (adjusted $P = .97$). Numerically, axi-cel demonstrated the highest 1-year PFS rate (68.2%). In older patients, PFS was comparable across the 3 products ($P = .75$; Figure 2B).

For progression rates, significant differences were observed among CAR-T products in younger patients ($P < .001$; Figure 2C). Pairwise analyses showed that axi-cel and liso-cel were both associated with significantly lower progression rates than tisa-cel (adjusted $P = .012$; adjusted $P = .005$), whereas no significant

Table 1. Patient characteristics

Factor	Age <65 y (n = 529)	Age ≥65 y (n = 379)	*P* value
Sex, n (%)			
Female	248 (46.9)	148 (39.1)	.021*
Male	281 (53.1)	231 (60.9)	
CAR product type, n (%)			
Axi-cel	56 (10.6)	50 (13.2)	.014*
Liso-cel	120 (22.7)	112 (29.6)	
Tisa-cel	353 (66.7)	217 (57.3)	
KPS, n (%)			
80	62 (14.1)	63 (21.8)	.009*
90-100	378 (85.9)	226 (78.2)	
Unknown	89	100	
Histological type, n (%)			
DLBCL	399 (75.4)	286 (75.5)	<.001*
tFL	81 (15.3)	73 (19.3)	
HGBCL	22 (4.2)	19 (5.0)	
PMBCL	27 (5.1)	1 (0.3)	
Disease status at CAR-T, n (%)			
CR	121 (22.9)	86 (22.7)	.39
PR	162 (30.7)	113 (29.8)	
SD/PD	150 (28.4)	127 (33.5)	
Non-CR untreated	27 (5.1)	14 (3.7)	
Non-CR sensitivity unknown	68 (12.9)	39 (10.3)	
Unknown	1	0	
Serum LDH level (IU/L), n (%)†			
<300	356 (74.9)	273 (73.8)	.75
≥300	119 (25.1)	97 (26.2)	
Unknown	54	9	
Preinfusion extranodal site, n (%)			
No	270 (59.9)	193 (58.1)	.66
Yes	181 (40.1)	139 (41.9)	
Unknown	78	47	
History of allogeneic stem cell transplantation, n (%)			
No	487 (97.8)	364 (100.0)	.003*
Yes	11 (2.2)	0 (0.0)	
Unknown	31	15	
History of ASCT, n (%)			
No	353 (70.9)	301 (82.7)	<.001*
Yes	145 (29.1)	63 (17.3)	
Unknown	31	15	
No. of previous lines, n (%)			
≦2	83 (15.7)	91 (24.0)	.002*
≥3	445 (84.3)	288 (76.0)	
Unknown	1	0	

Benda, bendamustine; CR, complete response; Cy, cyclophosphamide; DLBCL, diffuse LBCL; Flu, fludarabine; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; PD, progressive disease; PMBCL, primary mediastinal LBCL; PR, partial response; SD, stable disease; tFL, transformed follicular lymphoma.

*Statistically significant.

†All laboratory values were obtained before lymphodepletion.

Table 1 (continued)

Factor	Age <65 y (n = 529)	Age ≥65 y (n = 379)	*P* value
Conditioning, n (%)			
Flu/Cy	463 (87.7)	325 (85.8)	.48
Benda	19 (3.6)	13 (3.4)	
Other	42 (8.0)	34 (9.0)	
None	4 (0.8)	7 (1.8)	
Unknown	1	0	
Neutrophils, × 10^9/L†			
Median (IQR)	1.96 (1.13-2.98)	2.07 (1.27-3.30)	.65
Unknown	36	7	
Lymphocytes, × 10^9/L†			
Median (IQR)	0.60 (0.34-0.99)	0.76 (0.43-1.12)	.42
Unknown	34	15	
Hemoglobin, g/dL†			
Median (IQR)	9.6 (8.5-11.1)	9.6 (8.7-10.9)	.97
Unknown	22	9	
Platelets, × 10^9/L†			
Median (IQR)	146 (81-211)	147 (88-204)	.88
Unknown	30	13	

Benda, bendamustine; CR, complete response; Cy, cyclophosphamide; DLBCL, diffuse LBCL; Flu, fludarabine; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; PD, progressive disease; PMBCL, primary mediastinal LBCL; PR, partial response; SD, stable disease; tFL, transformed follicular lymphoma.

*Statistically significant.

†All laboratory values were obtained before lymphodepletion.

difference was found between axi-cel and liso-cel (adjusted $P > .99$). Numerically, axi-cel had the lowest progression rate in this group. In older patients, progression rates were comparable across products ($P = .085$; Figure 2D).

For NRM, no significant differences were observed among the 3 CAR-T products in younger patients ($P = .44$; Figure 2E). In contrast, significant differences were observed in older patients ($P = .030$; Figure 2F). Pairwise analyses showed that axi-cel was associated with significantly higher NRM than tisa-cel (adjusted $P = .049$), whereas liso-cel did not differ significantly from either axi-cel (adjusted $P > .99$) or tisa-cel (adjusted $P = .12$).

Given these differences in baseline characteristics, we performed multivariate analyses within the younger and older subgroups. In younger patients, liso-cel was significantly associated with better OS than tisa-cel, and both liso-cel and axi-cel were significantly associated with better PFS (supplemental Table 7).

In contrast, in older patients, these product differences were not significant for either OS or PFS (supplemental Table 8). Taken together, these findings suggest that the superiority of liso-cel and axi-cel becomes attenuated in older patients.

We then examined treatment-related toxicities, with a focus on CRS and ICANS, stratified by CAR-T products and age groups. The incidence of all-grade and grade ≥3 CRS was consistently highest with axi-cel across both age groups (Figure 3A-B). Regarding all-grade ICANS, axi-cel was also associated with the highest incidence in both younger and older patients (28.6% and 34.0%, respectively; Figure 3C). The incidence of grade ≥3 ICANS was also the highest with axi-cel, particularly among older patients (19.1%). In contrast, the incidence of severe ICANS was low with tisa-cel and liso-cel, even among older patients, with rates of 3.7% and 4.7%, respectively (Figure 3D).

We further evaluated the impact of grade ≥3 ICANS within the axi-cel cohort (supplemental Figure 4). PFS did not differ significantly between patients with and without grade ≥3 ICANS ($P = .053$; supplemental Figure 4A). NRM was significantly higher among patients with grade ≥3 ICANS ($P = .016$; supplemental Figure 4B).

Discussion

This nationwide cohort study demonstrated the efficacy and safety of anti-CD19 CAR-T therapy for older patients with LBCL, with similar clinical outcomes to those of younger patients. One-year OS and PFS rates were similar across age groups. After adjustments for relevant clinical covariates, the multivariate analysis revealed that age ≥65 years did not correlate with OS, indicating that older patients achieved similar survival outcomes to those of younger patients. In contrast, age ≥65 years was independently associated with improved PFS, suggesting the presence of residual or unmeasured confounding factors in our analysis. Therefore, this finding should not be interpreted as indicating inherently superior PFS in older patients, but rather that age alone does not appear to adversely affect treatment outcomes.

The results obtained herein suggest that age should not preclude the use of CAR-T therapy for appropriately selected older patients, which is consistent with previous findings in real-world settings in other countries.[17-22] Importantly, our study extends these observations to an Asian cohort. These findings are also compatible with earlier Japanese real-world data from a smaller cohort limited to

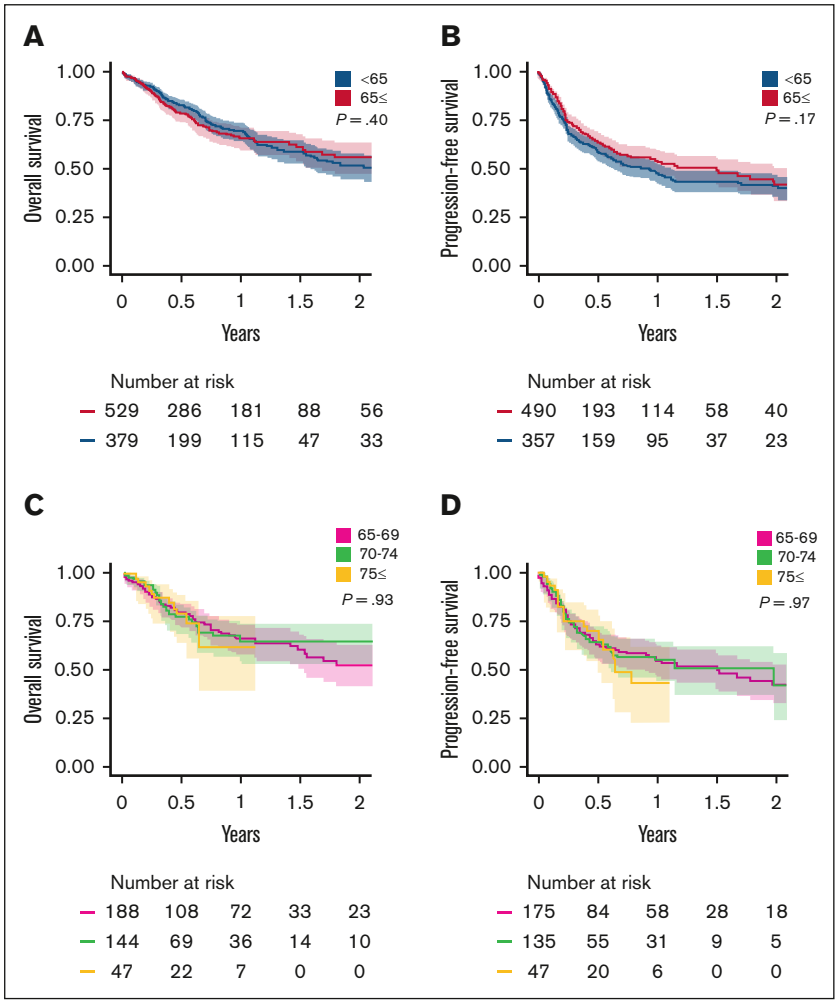

Figure 1. OS and PFS by age group. (A) OS and (B) PFS in patients aged <65 and ≥65 years. (C) OS and (D) PFS among older subgroups aged 65 to 69, 70 to 74, and ≥75 years.

tisa-cel recipients.[23] In real-world cohorts limited to patients aged ≥65 years,[24] OS did not differ between patients aged ≥75 years and those in the 65- to 69-year or 70- to 74-year age groups, which is consistent with our findings.

PS has been identified as a key prognostic factor in patients undergoing CAR-T therapy,[25,26] which is in agreement with the results of our multivariate analysis. In addition, comorbidity has been reported as an important predictor of clinical outcomes.[27] Therefore, PS and comorbidity may be more relevant than chronological age in decisions regarding eligibility and expected outcomes in older candidates for CAR-T therapy.

Our analysis revealed that the incidence of ICANS, including grade ≥3 events, was significantly higher in older patients than in younger patients. This result is consistent with previous findings showing an increased risk of neurotoxicity among older individuals receiving CAR-T therapy.[28-30]

The pathophysiology of ICANS is considered to be initiated by the release of proinflammatory cytokines from CAR-Ts and bystander myeloid cells, which contribute to systemic inflammation, ultimately leading to the disruption of the blood-brain barrier, immune cell infiltration, and neuroinflammation in the central nervous system.[31,32] Older patients may be particularly susceptible to this process due to age-associated changes in blood-brain barrier integrity, reduced neurovascular resilience, and underlying comorbidities. These physiological vulnerabilities may partially explain the significantly higher incidence of ICANS in older patients in our cohort. Therefore, close neurologic monitoring and proactive ICANS management are important for older patients receiving CAR-T therapy.

Our analysis also revealed notable differences in the distribution and outcomes of CAR-T products across age groups. In our study, both axi-cel and liso-cel demonstrated significantly superior PFS compared with tisa-cel in younger patients, in both univariate and multivariate analyses. Although axi-cel has been reported to provide superior PFS to tisa-cel,[33-35] our findings suggest that this advantage may be largely confined to younger patients.

Axi-cel incorporates a CD28 costimulatory domain, which has been associated with higher rates of ICANS,[33] particularly in older populations. In our cohort, patients who developed grade ≥3 ICANS within the axi-cel group had statistically significantly higher NRM. This may partially offset its disease control advantages in older patients, for whom neurotoxicity may pose greater clinical challenges. In our cohort, although no significant differences in PFS were observed among CAR-T products within the older subgroup, axi-cel was associated with significantly higher NRM than tisa-cel. Thus, given the increased risk of both neurotoxicity

Table 2. **Multivariate analyses for OS and PFS**

	OS		PFS	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age, y				
<65	Reference		Reference	
≥65	0.88 (0.65-1.21)	.44	0.73 (0.57-0.95)	.019*
Serum LDH level, IU/L†				
<300	Reference		Reference	
≥300	2.53 (1.84-3.48)	<.001*	1.63 (1.24-2.13)	<.001*
Preinfusion extranodal involvement				
No	Reference		Reference	
Yes	1.68 (1.20-2.35)	.002*	1.46 (1.11-1.92)	.007*
KPS				
90-100	Reference		Reference	
80	3.66 (2.61-5.13)	<.001*	2.18 (1.62-2.93)	<.001*
Disease status at CAR-T				
Non-CR	Reference		Reference	
CR	0.48 (0.29-0.80)	.005*	0.63 (0.44-0.89)	.009*
History of ASCT				
No	Reference		Reference	
Yes	0.58 (0.40-0.85)	.004*	0.51 (0.37-0.70)	<.001*
CAR-T product				
Tisa-cel	Reference		Reference	
Liso-cel	0.56 (0.36-0.87)	.010*	0.45 (0.31-0.65)	<.001*
Axi-cel	0.68 (0.35-1.33)	.27	0.56 (0.34-0.93)	.024*
No. of previous lines				
≤2	Reference			
≥3	1.37 (0.83-2.25)	.22	1.04 (0.73-1.49)	.82

CR, complete response.
*Statistically significant.
†LDH level was measured before lymphodepletion.

and NRM, careful consideration is warranted when selecting axi-cel for older patients.

This study has several limitations. First, as a real-world registry analysis, it is difficult to fully eliminate selection bias. Older patients who undergo CAR-T therapy are often carefully selected based on clinical judgment, and such unmeasured factors cannot be completely adjusted for. Therefore, the observed association between age ≥65 years and improved PFS should be interpreted only as suggesting that chronological age itself may not be a detrimental prognostic factor and likely reflects residual confounding that could not be fully accounted for, rather than indicating any inherent advantage in older patients. Second, detailed information on NRM, as well as several clinically relevant variables, including tumor burden, International Prognostic Index, and management of ICANS, was not available in the registry, limiting our ability to incorporate these factors into the analyses and to fully characterize treatment-related mortality or toxicity.

Table 3. **Adverse events**

Factor	**Age <65 y**	**Age ≥65 y**	***P* value**
CRS, n (%)	400/528 (75.8)	285/379 (75.2)	.876
CRS grade ≥3, n (%)	68/525 (13.0)	58/378 (15.3)	.331
ICANS, n (%)	37/528 (7.0)	48/379 (12.7)	.005*
ICANS grade ≥3, n (%)	15/518 (2.9)	22/368 (6.0)	.027*
1-Year NRM (cumulative incidence), % (95% CI)	4.3 (2.5-6.8)	8.2 (5.3-12.0)	.011*

*Statistically significant.

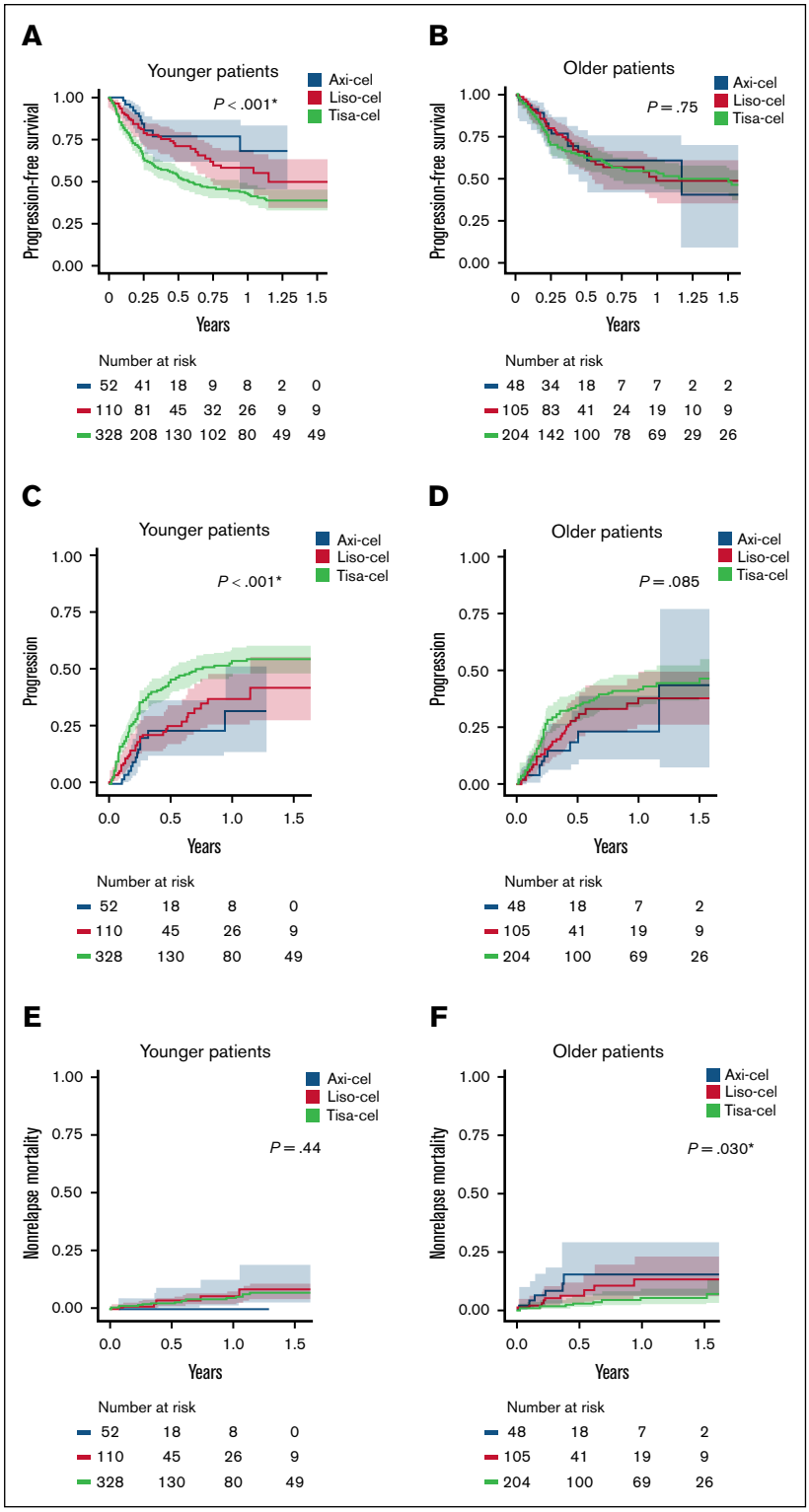

Figure 2. Comparative outcomes of different CAR-T products by age group. (A-B) PFS in younger patients (A) and older patients (B). (C-D) Cumulative incidence of progression in younger patients (C) and older patients (D). (E) NRM in younger patients and (F) older patients. Results are shown for axi-cel, liso-cel, and tisa-cel.

Finally, the number of patients treated with axi-cel was relatively small, particularly in subgroup analyses, which may reduce the precision and robustness of estimates for this product.

In this nationwide real-world cohort, CAR-T therapy for LBCL was shown to be safe and effective for older patients, including those aged ≥75 years. However, the incidence of ICANS was higher in

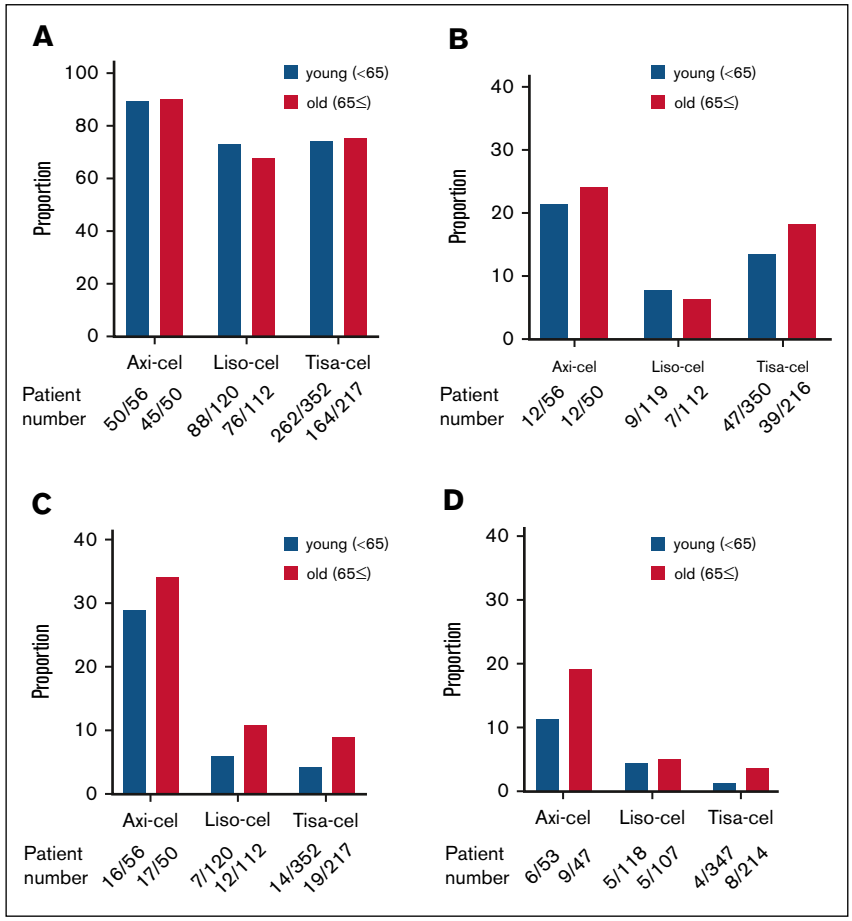

Figure 3. Incidence of CRS and ICANS by CAR-T product and age group. (A) CRS, all grades; (B) CRS, grade ≥3; (C) ICANS, all grades; (D) ICANS, grade ≥3. Data are shown for axi-cel, liso-cel, and tisa-cel in both younger and older patients.

older patients, underscoring the need for close neurologic monitoring and early interventions. Notably, the incidence of severe ICANS (grade ≥3) was also higher in older patients, highlighting its clinical relevance in this population.

Moreover, our analysis revealed that the impact of CAR-T products differed by age. Although axi-cel and liso-cel were associated with lower progression/relapse rates in younger patients, this benefit was attenuated in older patients. These findings underscore the need for careful individualization of product selection based on patient age and clinical risks.

Collectively, these results support the use of CAR-T therapy for appropriately selected older patients, while emphasizing the importance of toxicity management and product-specific considerations.

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Authorship

Contribution: S.S. and Y. Arai designed the study and performed data analysis and statistical evaluation; S.S. drafted the initial version of the manuscript; J. Kanda, D.K., D.M., and K. Kato critically reviewed and revised the manuscript; and T.K., K.S., T.S., S.Y., S.M., N.F., G.Y., E.S., Y.N., A.Y., Y.U., J. Kato, H.K., K. Kataoka, H.G., and Y. Atsuta contributed to data collection.

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