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THE INTERNATIONAL PROGNOSTIC INDEX IS ASSOCIATED WITH OUTCOMES IN DIFFUSE LARGE B CELL LYMPHOMA AFTER CAR T CELL THERAPY

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Abstract

CD19-targeted chimeric antigen receptor T cells (CAR T cells) have shown excellent activity against relapsed and refractory (R/R) diffuse large B-cell lymphoma (DLBCL). CAR T cell

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DISCLOSURE OF CONFLICTS OF INTEREST:

M.G.R. received honoraria from Janssen and Takeda. K.W., M.P., R.A.T., J.F., R.S., A.O.A, M.L.S., S.D., E.H., J.R., M.M. and E.M. have no relevant conflict of interest. P.D. has served as a paid consultant on advisory boards for Kite. C.W.B. has received research support from Janssen, Novartis, Epizyme, Xynomics and Bayer. She has served as a paid consultant on advisory boards for Life Sci, GLG, Juno/Celgene, Seattle Genetics and Kite. She received honoraria from Dava Oncology. S.G. has received consultant fees and honoraria related to speakers' bureau activities from Celgene Corporation, Genzyme Corporation, and Millennium Pharmaceuticals, Inc. L.P. is on the advisory committee of Pharmacyclics and provide consultancy for Noble insights. B.S. has consulted for Kite/Gilead, Juno/Celgene and Novartis. C.S.S. has served as a paid consultant on advisory boards for: Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite/a Gilead Company, Celgene, Gamida Cell and GSK. He has received research funds for clinical trials from: Juno Therapeutics, Celgene, Precision Biosciences and Sanofi-Genzyme. M.S. is a consultant for McKinsey & Company and Angiocrine Bioscience Inc. S.G. received research support from Amgen and Janssen. M.A.P. reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be the Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

therapy is associated with early toxicities, including cytokine release syndrome and neurotoxicity. The incidence and severity of these toxicities has in part been associated with baseline disease and patient characteristics, which may also impact overall survival (OS) and progression-free survival (PFS). However, there is limited data on patient selection and how to better predict toxicities or outcomes. Indexes used in DLBCL like the international prognostic index (IPI and age-adjusted IPI, aaIPI) and, in transplant, like the hematopoietic cell transplantation comorbidity index (HCT-CI) have not been evaluated in this setting. We evaluated 4 indexes (IPI, aaIPI, HCT-CI and the Charlson Comorbidity Index or CCI) and their associations with early CAR T cell related-toxicities and outcomes. We demonstrated an association between high-risk IPI or aaIPI and inferior PFS in patients with R/R DLBCL treated with CAR T cell therapies. We also found an association between aaIPI and IPI with OS and neurotoxicity, respectively. CCI was not associated with toxicities or outcomes and due to sample size, we could not conclude on associations with the HCT-CI. Both the IPI and aaIPI are widely used tools that can now provide better information to guide selection of patients who would best benefit from CD19 CAR T cell therapy.

Keywords

Chimeric antigen receptor T cells; cellular therapy; international prognostic index; non-Hodgkin lymphoma

INTRODUCTION:

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL) and represents up to 35% of adult NHL (1,2). While 10-year disease-free survival has been reported at 64%, outcomes after disease progression are poor, with 70% of deaths secondary to lymphoma within the first 2 years after disease progression (3,4). CD19-targeted chimeric antigen receptor T cells (CAR T cells) have shown excellent activity against B lymphoid malignancies, including relapsed/refractory (R/R) DLBCL (5–8).

The two most frequent early toxicities after the CAR T cell infusion are cytokine release syndrome (CRS) and neurotoxicity (9,10). CRS is a systemic inflammatory response triggered by *in vivo* CAR T cell expansion that can lead to fever, vascular instability, macrophage activation syndrome and multi-organ system toxicity (11). The severity of CRS is strongly associated with the severity of neurotoxicity. Neurological events may include headache, aphasia, tremor, encephalopathy, seizures or diffuse cerebral edema, among others. Severe CRS and neurotoxicity have been described with an incidence of 12–23% and 12–31%, respectively (12,13). There is currently limited published data that can guide patient selection for this treatment regarding both toxicities and outcomes. The international prognostic index (IPI) and the age-adjusted IPI (aaIPI) are two indexes used to identify DLBCL patients with a higher probability of survival (14). IPI has been validated for patients with DLBCL both in the frontline and salvage setting but not before CAR T cell therapy (15–17).

Salvage regimens for R/R DLBCL usually include consolidation with autologous stem cell transplantation (SCT)(18). In that context, the Charlson Comorbidity Index (CCI) (19) was

adapted and modified for patients undergoing hematopoietic cell transplantation (HCT) and renamed the HCT comorbidity index (HCT-CI), which has demonstrated an association between prior organ dysfunctions and non-relapse mortality (NRM) or overall survival (OS) after HCT (20). Neither the HCT-CI nor CCI have been evaluated in patients receiving CAR T cell therapy. This study aims to evaluate a possible association between indexes routinely used in the care of patients with R/R DLBCL (IPI, aaIPI, CCI and HCT-CI) and early toxicities and overall outcomes in DLBCL patients treated with FDA-approved CD-19 directed CAR-T cell therapy.

METHODS:

Study population

Between February 2018 and June 2019, all consecutive adult patients (age \geq 18 years old) diagnosed with R/R DLBCL who received FDA-approved CD19 CAR T cell products, axicebtogene ciloleuceel (axi-cel, Yescarta, Kite/Gilead) or tisagenlecleuceel (tisa-cel, Kymriah[®], Novartis), at our center were included in this study. Written informed consent was obtained from all patients before CAR T cell infusions. Approval for this retrospective study was obtained from our Institutional Review and Privacy Board.

CAR T cell infusion and supportive care

According to the product label, patients treated with tisa-cel received a lymphodepleting regimen consisting of fludarabine 25 mg/m² iv daily and cyclophosphamide 250 mg/m² iv daily for 3 days; or bendamustine 90 mg/m² iv for 2 days. Patients treated with axi-cel received fludarabine 30 mg/m² iv and cyclophosphamide 500 mg/m² iv for 3 days. All patients received supportive care and prophylaxis against opportunistic infections according to institutional guidelines.

Data collection and scoring

Data were collected from the institutional database and additional review of the electronic medical records. The IPI, aaIPI, HCT-CI and CCI were calculated as previously described (15,19,20), with the following modifications. The IPI and aaIPI were assessed based on serum lactate dehydrogenase (LDH), performance status and positron emission tomography (PET) imaging at the time of lymphodepletion, in order to have a homogeneous assessment of disease status given the wide spectrum of bridging therapies. Comorbidities were evaluated at the time of leukapheresis to calculate HCT-CI and CCI. Risk groups were stratified as in the original publications. Briefly, for the IPI, patients were classified into low-risk (IPI 0–1), low intermediate-risk (IPI 2), high intermediate-risk (IPI 3) and high-risk groups (IPI 4–5). For the aaIPI, patients were classified into low-risk (aaIPI 0), low intermediate-risk (aaIPI 1), high intermediate-risk (aaIPI 2) and high-risk groups (aaIPI 3). For the HCT-CI, patients were classified into low-risk (HCT-CI 0), intermediate-risk (HCT-CI 1–2) or high-risk groups (HCT-CI \geq 3). For the CCI, patients were classified into low-risk (CCI 0), intermediate-risk (CCI 1) and high-risk groups (CCI \geq 2). Patients without evaluable baseline disease status or pulmonary function tests (PFT) before cell infusion were excluded from the calculation of IPI and aaIPI or HCT-CI, respectively. Due to sample size, patients were clustered in two categories for each index except for the CCI: a low-risk category

(including low and low intermediate-risk groups for the IPI and aaIPI (21); and low and intermediate-risk groups for the HCT-CI), and a high-risk category (including high intermediate and high-risk groups for the IPI and aaIPI; and high-risk group for the HCT-CI). PET imaging was performed after completing bridging therapy, at day 30 and at day 90 after treatment. Outcome data was assessed per last known follow-up.

Definitions and endpoints

The primary endpoint of this study was to determine the association of aaIPI, IPI, CCI and HCT-CI with progression-free survival (PFS) after the CAR T cell infusion. Secondary endpoints were OS and the ability of the various indexes to detect early CAR T cell-related toxicities. PFS was defined as time until progression, death or last follow-up and OS was defined as time until death or last follow-up. Early CAR T cell-related toxicity was defined as the incidence of CRS or neurotoxicity (according to the American Society of Transplant and Cellular Therapy grading system) (22) within the first 30 days after the CAR T cell infusion.

Statistical analysis

A descriptive statistical analysis was used to summarize patient and disease characteristics. The Kaplan-Meier method was used to calculate OS and PFS. Univariate Cox proportional hazard regression model was used to investigate the association between the prognostic indexes evaluated (IPI, aaIPI, HCT-CI and CCI), each individual variable that compose them and outcomes (PFS and OS). Competing risks regression was used to evaluate the prognostic indexes and their association with early CAR T cell-related toxicities (neurotoxicity and/or CRS), where death was used as a competing event. Multivariate analysis was performed with the index with the highest significance in the univariate analysis (aaIPI) for PFS and OS. This analysis was adjusted for sex and age as covariates. All statistical analyses were performed using R, version 3.6.0.

RESULTS:

Patient characteristics

Between February 2018 and June 2019, 60 consecutive adult patients with R/R DLBCL who received FDA-approved CD19 CAR T cell products at our center were included (Table 1). Median age at the time of CAR T cell infusion was 63 (19–86). The majority of the patients were male (70%), with good performance status (PS 1 86.7%) and advanced disease stage (stage III or IV 85.0%). The underlying disease was DLBCL for all patients (41.7% transformed DLBCL and 58.3% de novo DLBCL). Histological subtypes and distribution of comorbidities are shown in table 1.

Seventeen patients had received a prior SCT (12 patients received a prior autologous SCT and 5 patients an allogeneic SCT). Axi-cel was the most commonly used CAR T cell product (71.6%) and the combination of fludarabine and cyclophosphamide (FluCy) was the most common lymphodepleting chemotherapy for both products. Baseline characteristics of patients receiving axi-cel and tisa-cel are described in table 1. The median follow-up was 206 days (24–562).

Prognostic indexes and risk stratification

We examined the associations of 4 indexes (IPI, aaIPI, HCT-CI and CCI) in patients receiving FDA-approved CD19 CAR T cell products with early CAR T cell related-toxicities and outcomes. Risk stratification for each index is summarized in table 2.

PET imaging was performed after completing bridging therapy in all patients except 8. The remaining 52 patients had all risk factors included in the IPI and aaIPI available, and were included in the analysis. The median IPI and aaIPI score were 3 (0–5) and 2 (0–3), respectively.

PFTs were not routinely required prior to a CAR T cell treatment, so pulmonary impairment could not be formally evaluated in most patients. Consequently, only 15 patients were evaluable for all 17 comorbidities included in the HCT-CI. The prevalence of comorbidities is shown in table 1. Mild hepatic alterations were the most frequent comorbidity (10/15, 66.6%) followed by arrhythmia (9/15, 60%), heart valve disease (9/15, 60%) and infections (9/15, 60%). Other cardiac events, psychiatric disturbances and obesity were present in more than half of the evaluable population. Median HCT-CI score was 1 (0–9). Risk stratification at the time of leukapheresis was as follows, 3 (20%) were low risk, 5 (33.3%) were intermediate risk and 7 (46.7%) were high risk HCT-CI. Due to sample size, cases were grouped into two categories: a low-risk category (HCT-CI <3, n=8, 53.3%) and a high-risk category (HCT-CI ≥3, n=7, 46.7%). Since the HCT-CI could only be assessed in a minority of patients, we also evaluated the CCI. Each of the 19 comorbidities included in the CCI could be assessed in all 60 patients (table 1). Similar to the HCT-CI, mild liver disease was the most prevalent comorbidity (16.7%). Myocardial infarct, connective tissue disease and diabetes were present in 10%. Median CCI score was 0 (0–7). Thirty-five patients (58.3%) were low risk, 12 (20%) were intermediate risk and 13 (21.7%) were high risk.

Progression free and overall survival

At last follow-up, 33 patients were alive with no evidence of disease, and 41 patients were alive. The probability of PFS at 3 and 6 months was 68.3% (95% CI 57.5%–81.2%) and 59.5% (95% CI 48.2%–73.5%), respectively. The probability of OS at 3 months and 6 months for our series was 88.3% (95% confidence interval (CI), 80.6–96.8) and 76% (95% CI, 65.7–87.8), respectively.

In the univariate analysis, both IPI ≥3 and aaIPI ≥2 were associated with inferior PFS (HR 2.86 [95% CI 1.09–7.48], p=0.026 and HR 6.19 [95% CI 2.07–18.5], p<0.001, respectively) when compared to their references (IPI<2 and aaIPI<1, respectively). For the other indexes tested, no significant differences were found when compared with their reference groups. (Table 3 and figures 1A and 1B). aaIPI ≥2 was the only risk factor for a lower OS (HR 7.39 [95% CI 1.64–32.22], p = 0.002, when compared to its reference (aaIPI <2). For the other indexes tested, no significant differences were found when compared with their reference groups (Table 3, Figure 1D). Each variable included in the evaluated indexes was tested in a univariate analysis for PFS and OS. In this analysis, LDH was the variable with the highest significance for PFS (Table 4).

Since the aaIPI was identified as the index with the highest significance in the univariate analysis, multivariate models were performed with aaIPI for PFS and OS. In the multivariate analysis, aaIPI ≥ 2 was associated with inferior PFS (HR 6.76 [95% CI 2.21–20.69], $p=0.001$) and OS (HR 7.91 [95% CI 1.74–35.85], $p=0.007$) (Table 3).

CAR T cell-related toxicities and ICU admission

Forty-four (73.3%) patients developed CRS ($n=44$, 73.3%, median grade 2 [1–4]) or neurotoxicity ($n=23$, 38.3%, median grade 3 [1–4]) during the first 30 days after the CAR T cell infusion. Sixteen (26.7%) patients required admission to the intensive care unit (ICU). The median length of stay in the ICU was 5 days (1–12). All patients admitted to the ICU had CRS (median grade of 2 [2–4]) and 14 (87.5%) patients had neurotoxicity (median grade 3 [1–4]).

In the univariate analysis for any toxicity, HCT-CI ≥ 3 was associated with higher incidence of CRS or neurotoxicity (HR 3.53 [95% CI 1.24–10.05], $p=0.018$) (Table 5). For the other indexes tested, no significant differences were found when compared with their reference groups. In the univariate analysis for CRS, HCT-CI ≥ 3 was associated with higher incidence of CRS (HR 3.53 [95% CI 1.24–10.05], $p=0.018$). Other indexes showed no significant differences when compared with their reference groups. The univariate analysis for neurotoxicity was significant for an association between IPI ≥ 3 and higher incidence of neurotoxicity (HR 2.53 [95% CI 1.01–6.38], $p=0.048$) when compared with its reference group (IPI <2). Other indexes showed no significant differences when compared with their reference groups.

No significant differences were found for any index tested when compared with their reference groups in the univariate analysis for severe CRS or severe neurotoxicity (Table 5).

DISCUSSION:

Prognostic indexes routinely used in patients with aggressive NHL such as IPI or aaIPI (15,23–25), or those commonly used in SCT recipients like the HCT-CI (20,26–29) are not routinely implemented in patients receiving commercial CD19 CAR T cell products. Other comorbidity indexes like the CCI (19) have not yet been studied in this setting either. In the present report, we demonstrate the association of IPI and aaIPI with PFS in patients with R/R DLBCL treated with commercial CAR T cell products. The aaIPI also is associated with OS, while the IPI is associated with neurotoxicity. Furthermore, in a subset of patients where it was evaluable, the HCT-CI was associated with early toxicity after CAR T cells infusion.

LDH is a risk factor included in both the IPI (age, tumor stage, LDH, performance status or PS and number of extranodal disease sites) and aaIPI (tumor stage, LDH and PS). In our study, of all indexes evaluated, aaIPI has the strongest association with PFS and OS ($p=0.001$ and $p=0.002$, respectively). This fact can be explained by the prominent weight of LDH in this index over the others. Different groups have identified LDH as a relevant prognostic factor in patients with R/R NHL treated with CAR T cell products. A recent analysis of patients' baseline characteristics and their association with treatment efficacy in

the Juliet trial showed that high levels of pre-infusion LDH, pre-infusion grade 3–4 thrombocytopenia, and grade 3–4 neurotoxicity were associated with inferior outcomes (PFS and OS)(30). In a comparative study of patients with R/R NHL treated with autologous stem cell transplantation (ASCT) vs. CD19 CAR T cell therapy (31), the only independent unfavorable factor for both PFS and OS was an elevated LDH level ($p = 0.012$ and $p = 0.005$, respectively). Interestingly, other risk factors like age, disease stage, or IPI 3 had no statistical significance in the multivariate analysis for OS in this study. However, the sample of patients included was small, and cases included had different histologies with different prognosis. In our series, the majority of patients had a good PS with advanced disease stage, reinforcing the role of LDH as outcome predictor.

Recently, Hirayama et al (32) also reported the association between an elevated pre-lymphodepletion LDH level and poor outcomes (PFS) in patients with R/R aggressive NHL receiving CD19 CAR T cells. Furthermore, this group identified a favorable cytokine profile at day 0 (defined as elevated monocyte chemoattractant protein-1, MCP-1, and IL-7) that could overcome the negative impact of an elevated LDH on PFS. An intense lymphodepletion regimen was associated with a higher probability of presenting a favorable cytokine profile. Other biomarkers that have been identified to impact outcomes are CRP < 30 mg/L and peak ferritin < 5.000 $\mu\text{g/L}$, both associated with improved PFS and OS(33).

PS 2, elevated LDH, soft tissue involvement or high metabolic tumor volume (MTV) are variables negatively associated with outcomes after CAR T cells (34–36). The impact of age, however, remains controversial. While a subanalysis of the 2-year follow-up of the ZUMA-1 trial showed survival rates are unaffected by age (37), a real-life study showed a negative tendency in the outcomes of young patients (34). This controversy supports our results favoring aaIPI over IPI as an outcome predictor, which also contrasts with the original publication of the scores (15). We cannot however exclude selection bias, particularly when it comes to older patients treated with these potentially toxic therapies.

Regarding early CD19 CAR-T cell therapy toxicities, we now show an association between high risk IPI and the development of neurotoxicity in patients with DLBCL treated with CD19 CAR T cells. In line with our results, other groups have studied IPI in lymphoma patients treated with CD19 CAR T cells and found no association between the IPI risk groups and the incidence of CRS (38). As the development of early toxicities seems to be related with the *in vivo* CAR T cell expansion after antigen recognition (39–41), it is not surprising that tumor burden, the intensity of lymphodepletion chemotherapy and CAR T cell dose have been identified as risk factors for CRS and neurotoxicity (42,43). Other factors associated with toxicity include thrombocytopenia before lymphodepletion for CRS (44), and pre-existing neurological comorbidity for neurotoxicity (45). Both severe CRS and neurotoxicity have also been associated with high levels of IL-6, IFN- γ , IL-15 and ferritin at baseline, before lymphodepletion (46,47). The effect of age on toxicity has also been analyzed. A recent real-world analysis based on the FDA Adverse Events Reporting System (FAERS) database of commercial CAR T cells a higher incidence of neurotoxicity (50% vs 39%, $p = 0.04$) in patients over 65, while younger patients (<65) had a higher incidence of CRS (80% vs 67%, $p < 0.01$) (48). A prognostic model of neurotoxicity after axi-cel that

combined clinical and laboratory factors, age was significantly associated with the development of neurotoxicity (49).

Finally, we also studied two well-known indexes in the transplant setting: the CCI and HCT-CI. While the CCI is a comorbidity index used to predict mortality in different malignancies (19), it includes comorbidities rarely present in SCT patients and also has limitations capturing comorbidities frequently present in these patients. Thus, in 2005 CCI was adapted to the transplant setting with the development of the HCT-CI (20). The HCT-CI is a helpful tool for selecting patients for SCT as it predicts NRM and survival after transplant. In order to calculate the HCT-CI, however, baseline testing needs to include PFTs and an echocardiogram, tests that are not typically required before a CAR T cell infusion. Consequently, only 15 of the 60 patients included were evaluable for the HCT-CI. Despite HCT-CI being associated with higher incidence of early toxicity after treatment in our study, we cannot draw definitive conclusions due to the small sample size. In addition, the patients who had PFTs and an echocardiogram performed may have represented a sicker group of patients as they had higher incidence of comorbidities than the full cohort. Furthermore, other groups tested HCT-CI in larger cohorts without finding a correlation with toxicity or outcomes (50). As expected, considering the limitations of the score, we did not find any association between CCI and the incidence of toxicities or outcomes.

Limitations of this study include the retrospective nature of the data collection and the small sample size available to evaluate HCT-CI.

In conclusion, we demonstrate a relationship between the IPI and aaIPI and PFS in patients with R/R DLBCL treated with commercial CD19 CAR T cells, demonstrating the relevance of these indexes as prognostic models in this patient population. Furthermore, we found that aaIPI is also associated with OS and IPI with the development of neurotoxicity in these patients. IPI and aaIPI are two simple and widely used tools in the management of aggressive NHL patients that can now provide better information to predict who would best benefit from CD19 CAR T cell therapy.

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HIGHLIGHTS

- High-risk IPI and aaIPI are associated with poor PFS in R/R DLBCL after CAR T cells
- High-risk aaIPI is associated with inferior OS in R/R DLBCL after CAR T cells
- High-risk IPI is associated with neurotoxicity in R/R DLBCL after CAR T cells

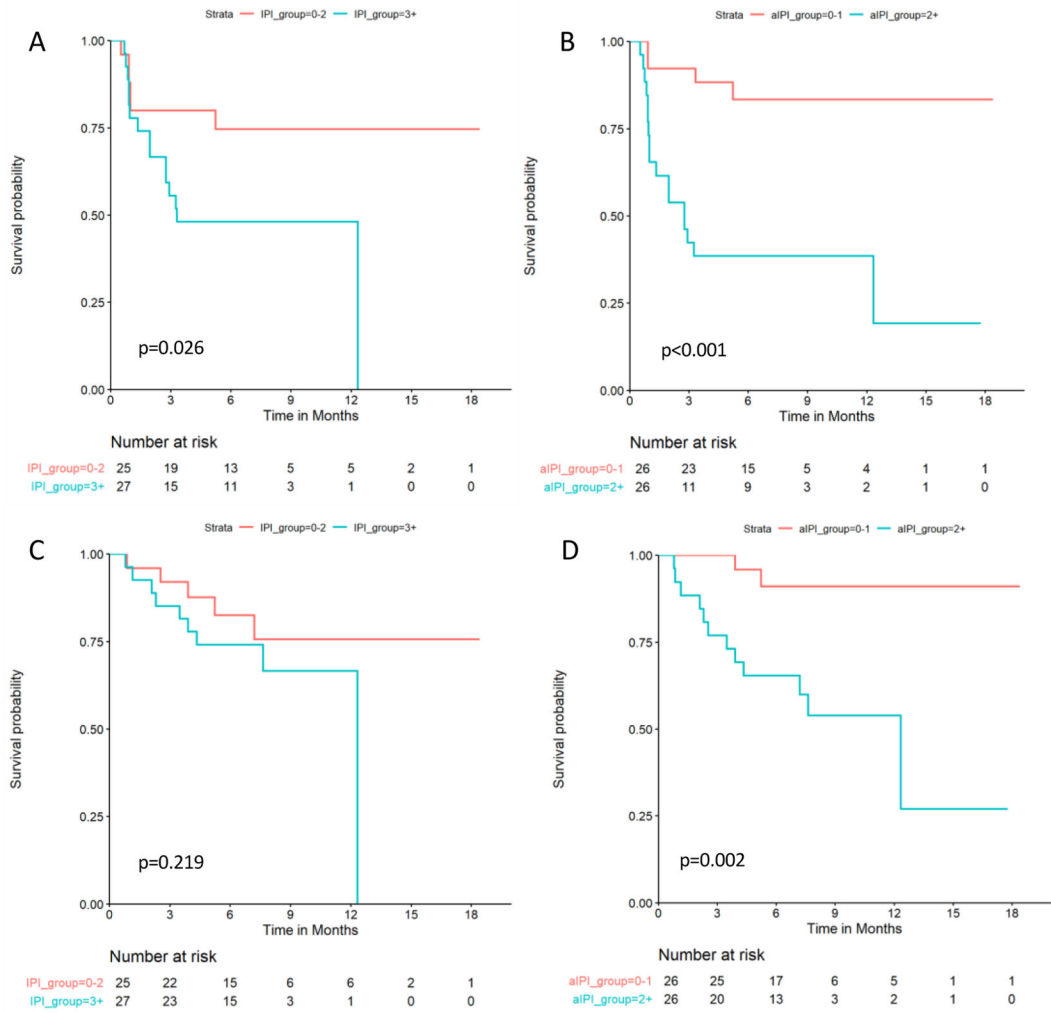


Figure 1. Survival Kaplan-Meier curves. Progression free survival curves for IPI (A) and aaPI (B). Overall survival curves for IPI (C) and aaPI (D).

Table 1.

Patient characteristics

Characteristics	Axi-cel	Tisa-cel	All	
Number of patients	43 (71.7%)	17 (28.3%)	60 (100%)	
Median age, years old (range)	61 (19–78)	71 (45–85)	63 (19–85)	
- N° of patients 60 years old	20 (33.3%)	4 (23.5%)	24 (40%)	
- N° of patients > 60 years old	23 (53.4%)	13 (76.4%)	36 (60%)	
Gender				
- Male	35 (81.4%)	7 (41.2%)	42 (70%)	
- Female	8 (18.6%)	10 (58.8%)	18 (30%)	
Performance status <1	36 (83.7%)	16 (94.1%)	52 (86.7%)	
Underlying disease				
- De novo DLBCL	24 (55.8%)	11 (64.7%)	35 (58.3%)	
- Transformed DLBCL	19 (44.2%)	6 (35.3%)	25 (41.7%)	
<i>Histological subtypes</i>				
- DLBCL, subtype Germinal Center B-cell	19 (44.2%)	6 (35.3%)	25 (41.7%)	
- DLBCL, subtype Non-Germinal Center B-cell	14 (32.5%)	10 (58.8%)	24 (40%)	
- High grade lymphoma B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements	5 (11.6%)	1 (5.9%)	6 (10%)	
- Other subtypes	5 (11.6%)	0 (0%)	5 (8.3%)	
N° patients with calculable stage*	38	14	52	
- Stage III or IV	35 (92.1%)	10 (71.4%)	45 (86.5%)	
Elevated LDH	24 (63.1%)	6 (35.3%)	30 (50%)	
Prior autologous transplant	9 (20.9%)	3 (17.6%)	12 (20%)	
Prior allogeneic transplant	5 (11.6%)	0 (0%)	5 (8.3%)	
Lymphodepleting regimen				
- FluCy	43 (100%)	14 (82.3%)	-	
- Bendamustine	-	3 (17.6%)	-	
Comorbidities	Axi-cel (n=43)	Tisa-cel (n=17)	All patients (n=60)	Calculable HCT-CI (n=15)
- Arrhythmia	5 (11.6%)	4 (23.5%)	9 (15%)	3 (20%)
- Cardiac	5 (11.6%)	3 (17.6%)	8 (13.3%)	2 (13.3%)
- Inflammatory bowel disease	0 (0%)	1 (5.9%)	1 (1.6%)	0 (0%)
- Diabetes Mellitus	5 (11.6%)	1 (5.9%)	6 (10%)	3 (20%)
o Diabetes Mellitus with end organ damage	2 (4.6%)	0 (0%)	2 (3.3%)	1 (6.6%)
- Cerebrovascular disease	1 (2.3%)	1 (5.9%)	2 (3.3%)	1 (6.6%)
- Psychiatric disturbance	6 (13.9%)	2 (11.8%)	8 (13.3%)	0 (0%)
- Hepatic impairment, mild	8 (18.6%)	2 (11.8%)	10 (16.6%)	3 (20%)
- Obesity	7 (16.3%)	1 (5.9%)	8 (13.3%)	3 (20%)
- Infection	7 (16.3%)	2 (11.8%)	9 (15%)	1 (6.6%)
- Rheumatologic disorders	4 (9.3%)	2 (11.8%)	6 (10%)	2 (13.3%)
- Peptic ulcer	3 (7%)	1 (5.9%)	4 (6.6%)	1 (6.6%)
- Moderate/severe renal abnormalities	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Chronic pulmonary disease ¹	4 (9.3%)	0 (0%)	4 (6.6%)	2 (13.3%)
- Moderate pulmonary ¹	2 (4.6%)	2 (11.8%)	4 (6.6%)	4 (26.6%)
- Prior solid tumor	3 (7%)	3 (17.6%)	6 (10%)	0 (0%)
- Any solid tumor during the last 5 years	2 (4.6%)	1 (5.9%)	3 (5%)	0 (0%)
- Heart valve disease	6 (13.9%)	3 (17.6%)	9 (15%)	2 (13.3%)
- Severe pulmonary ¹	4 (9.3%)	0 (0%)	4 (6.6%)	4 (26.6%)
- Moderate/severe hepatic impairment	1 (2.3%)	0 (0%)	1 (1.6%)	0 (0%)

¹Diagnosis based on clinical symptoms. DLBCL: Diffuse large B-cell lymphoma, LDH: Lactate dehydrogenase.

Table 2.

Prognostic scores

	N (%)
IPI (n=52)	
- low-risk group	8 (15.4%)
- low intermediate-risk group	17 (32.7%)
- high intermediate-risk group	20 (38.5%)
- high-risk group	7 (13.5%)
<i>Adapted categories</i>	25 (48.1%)
- low-risk category	27 (51.9%)
- high-risk category	
aaIPI (n=52)	
- low-risk group	4 (7.7%)
- low intermediate-risk group	22 (42.3%)
- high intermediate-risk group	22 (42.3%)
- high-risk group	4 (7.7%)
<i>Adapted categories</i>	26 (50%)
- low-risk category	26 (50%)
- high-risk category	
HCT-CI (n=15)	
- low-risk group	3 (20%)
- intermediate-risk group	5 (33.3%)
- high-risk group	7 (46.7%)
<i>Adapted categories</i>	8 (53.3%)
- low-risk category	7 (46.7%)
- high-risk category	
CCI (n=60)	
- low-risk group	34 (56.7%)
- intermediate-risk group	14 (23.3%)
- high-risk group	12 (20%)

IPI: International Prognostic Index, aaIPI: Age adjusted Intenational Prognostic Index, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, CCI: Charlson Comorbidity Index

Table 3.

Univariate and multivariate analysis for outcomes

Univariate analysis for PFS and OS				
	Progression Free Survival		Overall survival	
	Hazard Ratio (95%CI)	P-value	Hazard Ratio (95%CI)	P-value
IPI - 0-2 - 3-5	1 2.86 (1.09-7.48)	0.026	1 2 (0.65-6.14)	0.219
aaIPI - 0-1 - 2-3	1 6.19 (2.07-18.5)	0.001	1 7.39 (1.64-33.22)	0.002
HCT-CI - 0-2 - 3	1 0.63 (0.14-2.86)	0.544	1 1.58 (0.26-9.53)	0.614
CCI - 0 - 1 - 2	1 0.79 (0.29-2.19) 1.35 (0.55-3.32)	0.648	1 1.2 (0.37-3.89) 2.23 (0.78-6.36)	0.298
Multivariate analysis for PFS and OS				
	Progression Free Survival		Overall survival	
	Hazard Ratio (95%CI)	P-value	Hazard Ratio (95%CI)	P-value
aaIPI - 0-1 - 2-3	1 6.76 (2.21-20.69)	0.001	1 7.91 (1.74-35.85)	0.007

IPI: International Prognostic Index, aaIPI: Age adjusted International Prognostic Index, HCT-CI: Hematopoietic Transplant Comorbidities Index, CCI: Charlson Comorbidity Index

Table 4.

Univariate analysis of patient characteristics for outcomes

Univariate analysis for PFS and OS						
	Progression Free Survival			Overall survival		
	Hazard Ratio (95%CI)	P-value	Q-value	Hazard Ratio (95%CI)	P-value	Q-value
Age >60	0.72 (0.34–1.55)	0.4	0.8	0.52 (0.21–1.28)	0.2	0.4
High LDH	5.32 (2.13–13.3)	<0.001	0.008	6.55 (1.90–22.5)	0.003	0.069
Stage III/IV	3.85 (0.51–28.8)	0.2	0.8	-	-	-
PS 1	1.67 (0.63–4.41)	0.3	0.8	2.21 (0.73–6.74)	0.2	0.4
NET > 1	1.93 (0.80–4.65)	0.14	0.8	2.21 (0.74–6.60)	0.2	0.5
Presence of arrhythmias	0.57 (0.17–1.92)	0.4	0.8	0.28 (0.04–2.10)	0.2	0.5
Cardiac issues	1.17 (0.4–3.38)	0.8	>0.9	1.39 (0.40–4.79)	0.6	0.7
Diabetes	1.17 (0.35–3.9)	0.8	>0.9	2.45 (0.69–8.67)	0.2	0.4
Cerebrovascular disease	1.61 (0.37–6.88)	0.5	0.8	1.01 (0.13–7.64)	>0.9	>0.9
Psychiatric disturbance	1.38 (0.52–3.65)	0.5	0.8	1.75 (0.58–5.34)	0.3	0.5
Hepatic, mild	2.49 (0.74–8.40)	0.14	0.7	6.35 (1.71–23.6)	0.006	0.07
Obesity	0.67 (0.20–2.24)	0.5	0.8	0.52 (0.12–2.33)	0.4	0.6
Infection	1.58 (0.64–3.92)	0.3	0.8	2.12 (0.75–5.98)	0.2	0.4
Rheumatologic	1.07 (0.32–3.57)	>0.9	>0.9	2.02 (0.58–6.99)	0.3	0.5
Peptic ulcer	2.08 (0.62–6.96)	0.2	0.8	2.06 (0.47–9.10)	0.3	0.5
Moderate/severe renal	2.26 (0.30–16.8)	0.4	0.8	1.87 (0.24–14.7)	0.6	0.7
Prior solid tumor	1.07 (0.32–3.56)	>0.9	>0.9	0.46 (0.06–3.49)	0.5	0.6
Heart valve disease	0.89 (0.31–2.58)	0.8	>0.9	1.10 (0.32–3.80)	0.9	>0.9
Severe pulmonary	1.73 (0.52–5.77)	0.4	0.8	2.28 (0.65–8.01)	0.2	0.5
Moderate/severe hepatic	3.72 (0.87–16)	0.07	0.6	3.62 (0.8–16.3)	0.09	0.4
Variables only included in CCI						
Myocardial infarct	1.43 (0.49–4.13)	0.5	0.8	1.67 (0.48–5.78)	0.4	0.6
Chronic pulmonary disease	0.57 (0.08–4.19)	0.6	0.8	0.72 (0.09–5.52)	0.8	0.8
Connective tissue disease	1.07 (0.32–3.57)	>0.9	>0.9	2.02 (0.58–6.99)	0.3	0.5
Diabetes with end-organ damage	0.93 (0.13–6.86)	>0.9	>0.9	1.66 (0.22–12.5)	0.6	0.7
Any Solid tumor last 5y	0.69 (0.09–5.11)	0.7	>0.9	-	-	-

Inflammatory bowel disease, moderate pulmonary impairment, congestive heart failure, peripheral vascular disease, dementia, hemiplegia, metastatic solid tumor and AIDS could not be evaluated due to the low incidence of cases in our series. Empty cells correspond to variables that do not converge for the model tested.

Table 5.

Univariate analysis for toxicities

Univariate analysis for CRS ¹ and neurotoxicity combined								
	CRS and NTX				CRS and NTX			
	Hazard Ratio (95%CI)		P-value		Hazard Ratio (95%CI)		P-value	
IPI - 0-2 - 3-5	1 1.45 (0.83-2.53)		0.186		1 1.69 (0.55-5.19)		0.361	
a-IPI - 0-1 - 2-3	1 1.1 (0.63-1.92)		0.733		1 2.72 (0.79-9.37)		0.113	
HCT-CI - 0-2 - 3	1 3.53 (1.24-10.05)		0.018		1 2.16 (0.43-10.75)		0.347	
CCI - 0 - 1 - 2	1 1.54 (0.83-2.86) 1.53 (0.77-3.05)		0.27		1 2.11 (0.71-6.3) 0.71 (0.15-3.32)		0.291	
Univariate analysis for each toxicity								
	CRS		CRS grade 3-4		NTX		NTX grade 3-4	
	Hazard Ratio (95%CI)		P-value		Hazard Ratio (95%CI)		P-value	
IPI - 0-2 - 3-5	1 1.22 (0.69-2.16)		0.505		1 2.39 (0.47-12.09)		0.291	
a-IPI - 0-1 - 2-3	1 0.91 (0.51-1.63)		0.754		1 5.91 (0.71-49.32)		0.101	
HCT-CI - 0-2 - 3	1 3.53 (1.24-10.05)		0.018		1 0.53 (0.05-5.41)		0.589	
CCI - 0 - 1 - 2	1 1.27 (0.67-2.42) 1.3 (0.61-2.77)		0.666		1 2.84 (0.61-13.24) 0.93 (0.09-9.23)		0.357	
					1 2.1 (0.87-5.04) 0.99 (0.33-2.92)		0.205	
					1 1.46 (0.46-4.65)		0.525	
					1 1.75 (0.75-4.09)		0.197	
					1 4.2 (0.58-30.45)		0.155	
					1 2.24 (0.74-6.82) 0.82 (0.17-4.06)		0.275	

CRS: cytokine release syndrome; NTX: neurotoxicity. IPI: International Prognostic Index, aaIPI: Age adjusted International Prognostic Index, HCT-CI: Hematopoietic Transplant Comorbidities Index, CCI: Charlson Comorbidity Index