Impact and safety of chimeric antigen receptor T-cell therapy in older, vulnerable patients with relapsed/refractory large B-cell lymphoma

Large B-cell lymphoma (LBCL) predominantly affects older adults with generally suboptimal outcomes even when treated with curative intent.[1] In the relapsed/refractory setting, the outcome is dismal and effective treatment for these cases remains an unmet medical need.[2] The development of chimeric antigen receptor T-cell therapy (CAR T) has revolutionized the treatment of relapsed/refractory LBCL.[3] However, the impact and safety of this treatment in vulnerable, older patients with lymphoma, especially those with multiple comorbid conditions and functional limitation, has not been explored. These geriatric vulnerabilities have been associated with poor survival and increased treatment-related toxicities in older lymphoma patients receiving anthracycline-based chemoimmunotherapy.[1] The Centers for Medicare & Medicaid Services have recently proposed complete coverage for CAR T in Medicare beneficiaries, highlighting the significant need for older patients including those with geriatric deficits and frailty.

In this study, we examined the outcomes of older LBCL patients referred for treatment with commercial CAR T products, axicabtagene ciloleucel (Yescarta, Kite-Gilead) and tisagenlecleucel (Kymriah, Norvartis), at our institution, and explored the prevalence and impact of prospectively collected, baseline geriatric vulnerabilities. Importantly, we compared toxicities and outcomes of younger *versus* older patients who received CAR T using the Medicare coverage policy cutoff of 65 years. A multidimensional geriatric assessment of comorbidity burden, function, mobility, nutrition, mood, and medication was prospectively performed prior to CAR T by a geriatrician or by an interdisciplinary clinical provider, as previously described.[4] Specifically, the comorbidity burden was defined using the Deyo/Charlson Comorbidity Index (DCI/CCI).[5] Functional limitations were defined by deficits in basic or instrumental activities of daily living.[4] Cognitive impairment was defined by a score <26 on the Montreal Cognitive Assessment.[4]

A waiver of authorization for retrospective collection of demographic, treatment, and survival data was obtained from the Institutional Review and Privacy Board. Patients' referral data were collected from the central intake database from January 2018 to March 2019. All patients had a diagnosis of relapsed/refractory LBCL after two or more lines of systemic therapy. CAR T eligibility criteria, clinical care, and disease monitoring were in accordance with the Yescarta and Kymriah product inserts and standard institutional guidelines. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the American Society of Transplantation and Cellular Therapy consensus.[6,7]

Standard descriptive statistics were used, and comparisons were performed using the Fisher exact test or Wilcoxon rank-sum test where appropriate. The association between receipt of CAR T and post-relapse overall survival, defined as the time survived from last biopsy-proven relapsed/refractory state, was examined using univariable Cox proportional hazards regression with a time-dependent covariate accounting for time of initiation of CAR T. Overall survival and progression-free survival of the treated group were estimated from the date of CAR T infusion using the Kaplan-Meier method. All survival comparisons across groups were based on the log-rank test, except for the comparison between patients treated with CAR T and those who received other therapies, which was based on a Wald test. All statistical analyses were performed using SAS software version 9.4 (The SAS Institute, Cary, NC, USA).

Forty-two consecutive patients aged 65 years or older with relapsed/refractory LBCL were included in the analysis of post-relapse overall survival, including 24 patients who received CAR T and 18 who did not either because of clinical ineligibility as judged by physicians and/or death during the pre-requisite clinical evaluation. None of these 18 patients had undergone apheresis for a CAR T product. Instead, they received salvage chemotherapy or supportive care only. Age, gender, prior lines of therapy, relapse stage, comorbidity burden, and Karnofsky Performance Status were comparable in the two groups (*Online Supplementary Table S1*). With a median follow-up of 291 days (range, 162-572) for survivors, the group of older patients who had received CAR T had a lower risk of death compared to those who had not received CAR T (hazard ratio [HR] 0.31, 95% confidence interval [95% CI]: 0.10-0.93, P=0.04, for post-relapse overall survival).

During the same period in which the above 24 patients ≥65 years old were treated, an additional 25 patients <65 years old received CAR T for relapsed/refractory LBCL. All 49 patients met eligibility criteria for treatment with a commercial product and the use of bridging therapy was at the discretion of treating physicians. The median number of lines of prior therapy was 3 (range, 2-9); the median time from last relapse/disease progression to CAR T was 86 days (range, 33-272); and 42/49 (86%) of the patients were in relapse or had progressive disease prior to CAR T. Most patients had a pre-CAR T assessment of function, comorbidity, cognition, mobility, mood, and nutrition. Overall, the comorbidity burden was moderate (median DCI/CCI 2; range, 2-7); 27% of patients had functional limitation; 44% had cognitive impairment; 29% had had prior falls; 27% had weight loss; and 10% had depression at baseline (Table 1 and *data not shown*).

Baseline characteristics were similar in the two age groups including: Karnofsky Performance Status, functional limitations, cognition, mobility (prior falls), weight loss, and disease characteristics including prior lines of therapy, lactate dehydrogenase concentration, stage, and time to CAR T (Table 1). The older group included more females (P<0.001) and the patients had higher DCI/CCI values (P=0.04) (Table 1). Numerically more younger patients (84%) received axicabtagene ciloleucel than tisagenlecleucel (63%; P=0.11). We compared the safety and toxicity profiles between older and younger patients and found that the two groups had similar incidences of all grade and grade 3-4 cytokine release syndrome and ICANS (Table 1). Incidences of grade 3-4 hematologic and non-hematologic toxicities, as defined by Common Terminology Criteria for Adverse Events v5.0, were also similar between the two groups, although older patients appeared to have numerically fewer infections and cytopenia, and more metabolic and other toxicities (Table 1). The rate of intensive care unit admission was similar in the two age groups.

With a median follow-up of 179 days for survivors among these 49 CAR T patients (range, 84-470), the 6-month median progression-free and overall survival rates were 48% (95% CI: 33-63), and 71% (95% CI: 57-84), respectively. The 100-day complete response rate was 51%. Importantly, we did not observe evidence of a statistically significant difference in progression-free or overall survival between the older and younger groups of

Table 1. Characteristics and toxicities of lymphoma patients treated with chimeric antigen receptor T-cell therapy.

	Younger patients (<65 years, n=25)	Older patients (≥65 years, n=24)	P
Age in years, median (range)	56 (20 – 64)	72 (67 – 86)	
Female gender, n (%)	2 (8)	13 (54)	<0.001
CAR T, n (%)			0.11
Axicabtagene ciloleucel	21 (84)	15 (63)	
Tisagenlecleucel	4 (16)	9 (37)	
Advanced stage at CAR T, n (%)	14 (56)	14 (58)	0.78
Prior lines, median (range)	3 (2 – 9)	3 (2 – 9)	0.81
Baseline LDH, median (range)	298 (128 – 3722)	240 (146 – 1409)	0.12
Time to CAR T, median (range)	75 days (43 – 175)	92 days (33 – 272)	0.54
DCI/CCI, median, (range)	2 (2 – 4)	3 (2 – 7)	0.04
KPS <80, n (%)	7 (28)	9 (38)	0.55
Functional limitation, n (%)	5 (20)	8 (33)	0.35
Cognitive impairment, n (%)	8 (32)	11 (46)	0.76
Prior fall, n (%)	7 (28)	7 (29)	>0.99
Weight loss, n (%)	8 (32)	5 (21)	0.52
ICU admission, n (%)	9 (36)	6 (25)	0.54
CRS, n (%)			0.61
No CRS	7 (28)	4 (17)	
Grade 1-2 CRS	15 (60)	18 (75)	
Grade >2 CRS	3 (12)	2 (8)	
ICANS, n (%)			0.60
No ICANS	16 (60)	11 (46)	
Grade 1-2 ICANS	6 (24)	7 (29)	
Grade >2 ICANS	4 (16)	6 (25)	
Infections, ≥G3, n (%)	15 (60)	10 (42)	0.26
Prolonged cytopenia, n (%)	16 (64)	10 (42)	0.16
Metabolic toxicities, ≥ grade 3, n (%)	3 (12)	8 (33)	0.10
Other toxicities, ≥ grade 3, n (%)	9 (36)	12 (50)	0.39

CAR T: chimeric antigen receptor T-cell therapy; TimeCAR T: time (in days) from last relapse/disease progression to start of CAR T; LDH: lactate dehydrogenase; DCI/CCI: Deyo/Charlson Comorbidity Index; KPS: Karnofsky Performance Status; ICU: intensive care unit; CRS: cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome.

patients by either chronological age (Figure 1A, B), functional limitation, cognitive impairment, or comorbidity burden (DCI/CCI >2, *data not shown*). At the time of last follow-up, only one treatment-related death had occurred within 100 days: a 69-year old woman had died as a result of prolonged cytopenia. An additional patient with a history of prior allogeneic hematopoietic cell transplantation died of influenza pneumonia 129 days after CAR T infusion.

We present here for the first time, outcomes of older LBCL patients referred for CAR T in the context of geriatric vulnerabilities. Not surprisingly, we found that older patients who received CAR T had better post-relapse overall survival than those who were referred but not treated; it is likely that there was a selection bias for patients who did not have rapidly progressive disease, significant comorbidities, or suboptimal performance status. This could also explain why we did not have manufacture failures or deaths prior to infusion in this small cohort of patients. Interestingly, no excess toxicity was found in several real-world cohorts of CAR T patients including those with poor performance status in whom chemotherapy was historically associated with significant toxicity and mortality, adding to the complexity of selection of patients for CAR T.[8-10] Multicenter collaborative and registry studies are currently underway to prospectively identify geriatric impairments, to validate their prognostic impact, and to develop proper algorithms for the selection of patients.

While prior studies compared outcomes of CAR T based on chronological age alone,[11,12] we identified a significant burden of baseline geriatric vulnerabilities including functional limitations, multiple comorbid conditions, cognitive impairment, weight loss, decreased mobility, and polypharmacy in our patients. Importantly, our low treatment-related mortality and similar efficacy and toxicities across groups of patients of different chronological age and impairment suggest that older, vulnerable patients should be similarly considered for CAR T as younger patients. We acknowledge that while no major differences were seen between groups, we cannot rule out smaller differences due to small sample size and patient selection bias. Lastly, our findings also support the concept that reducing disease burden may help to improve function and performance status in older lymphoma patients.[13] Interestingly, while geriatric assessment domains such as functional limitation and multimorbidity are prognostically important for lymphoma

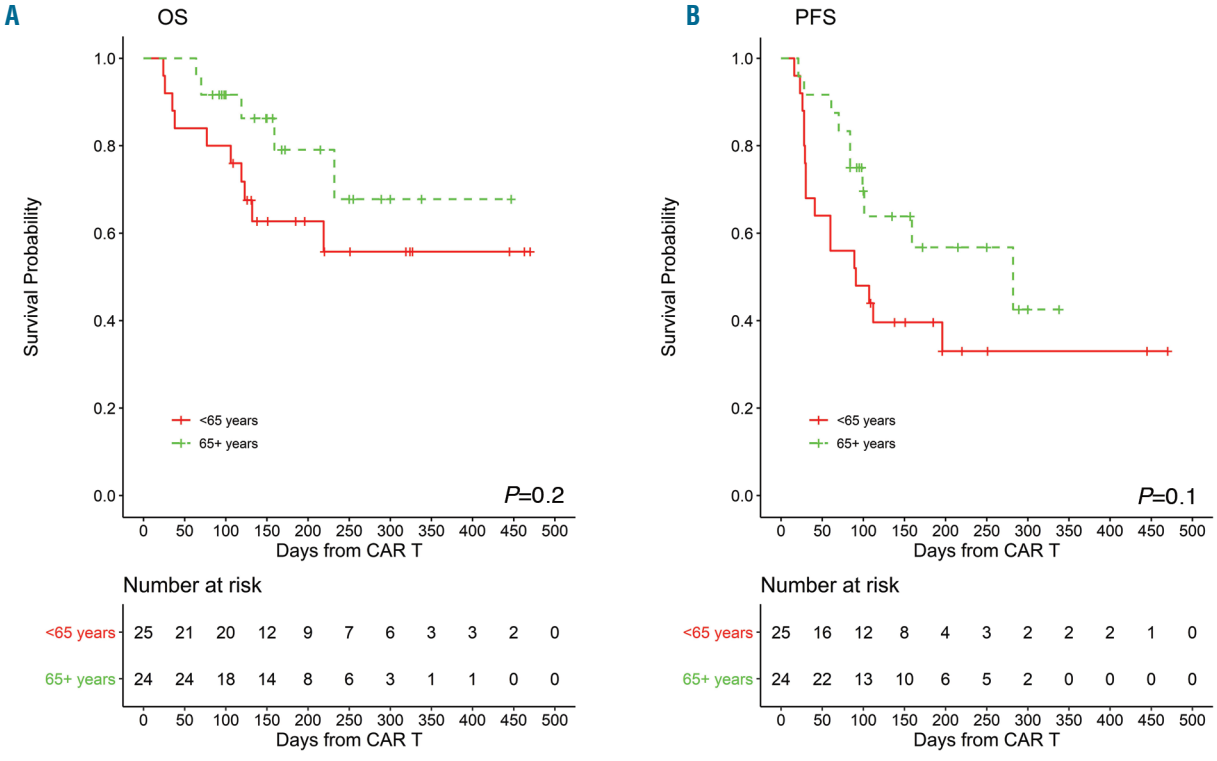

Figure 1. Survival outcomes. (A) Overall survival (OS) of lymphoma patients who were treated with chimeric antigen receptor T-cell therapy (CAR T) stratified by age. Green line: patients 65 years or older (n=24). Red line: patients younger than 65 years (n=25). Numbers at risk are tabulated. (B) Progression-free survival (PFS) of lymphoma patients who were treated with CAR T stratified by age. Green line: patients 65 years or older (n=24). Red line: patients younger than 65 years (n=25). Numbers at risk are tabulated.

patients undergoing chemoimmunotherapy or autologous transplantation,[1,14] they may not be prognostic in the setting of CAR T.

In summary, although limited by small sample size and likely patient selection bias, our results highlight potential benefits of CAR T without excessive cytokine release syndrome, ICANS, and other high-grade toxicities, in selected older patients. These findings extend beyond published results for older patients in the ZUMA-1 and JULIET trials, and provide novel insights and the entry point for large-scale investigation of geriatric vulnerabilities in patients considered for CAR T. We contend that older patients should not be automatically excluded from CAR T based solely on chronological age, multi-morbidity, functional limitation, or cognitive impairment; rather, their care should be individualized including greater attention to non-oncological geriatric issues. It is likely that a detailed geriatric assessment in combination with organ function evaluation will allow better selection of older patients who could benefit from this curative treatment.[15]

Richard J. Lin,[1,2] Stephanie M. Lobaugh,[3] Martina Pennisi,[1] Hei Ton Chan,[1,°] Yakup Batlevi,[1] Josel D. Ruiz,[1] Theresa A. Elko,[1] Molly A. Maloy,[1] Connie L. Batlevi,[2,4] Parastoo B. Dahi,[1,2] Sergio A. Giralt,[1,2] Paul A. Hamlin,[2,4] Elena Mead,[2,5] Ariela Noy,[2,4] M. Lia Palomba,[2,4] Bianca D. Santomasso,[2,6] Craig S. Sauter,[1,2] Michael Scordo,[1,2] Gunjan L. Shah,[1,2] Beatriz Korc-Grodzicki,[2,7] Soo Jung Kim,[7] Mari Lynne Silverberg,[1] Chelsea A. Brooklyn,[1] Sean M. Devlin[3] and Miguel-Angel Perales[1,2]

[1]Adult BMT Service, Memorial Sloan Kettering Cancer Center; [2]Department of Medicine, Weill Cornell Medical College; [3]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center; [4]Lymphoma Service, Memorial Sloan Kettering Cancer Center; [5]Critical Care Service, Memorial Sloan Kettering Cancer Center; [6]Neurology Service, Memorial Sloan Kettering Cancer Center and [7]Geriatrics Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

°Current address: Columbia University Medical Center, New York, NY, USA

Correspondence:
MIGUEL-ANGEL PERALES - peralesm@mskcc.org

doi:10.3324/haematol.2019.243246

Disclosures: SAG: advisory Board for Amgen, Actinuum, Celgene, Johnson & Johnson, Jazz pharmaceutical, Takeda, Novartis, Kite, Spectrum Pharma; research funding from Amgen, Actinuum, Celgene, Johnson & Johnson, Miltenyi, Takeda; CLB: research funding from Epizyme, Novartis, Janssen, BMS, Miragen, Mediimmune; consultancy from Defined Health; HTC: consultancy: Atara Biotherapeutics; GLS: research funding from Janssen and Amgen; MS: consultancy and research funding: Angiocrine Bioscience, Inc.; consultancy: McKinsey & Company; PAH: research support and consulting fees from Portola Pharmaceuticals, Inc. CSS: consultant on advisory boards for: Juno Therapeutics, Sanofi Genzyme, Spectrum Pharmaceuticals, Novartis, Precision Biosciences, Kite, a Gilead Company and GSK. Research funds for investigator-initiated trials from: Juno Therapeutics and Sanofi-Genzyme; AN: research funding from Pharmacyclics and Raphael. Honoraria from Prime Oncology, Medscape, and EUSA. Advisory Board for Janssen; MLP: advisory Board for Celgene, Consultant for Merck and Pharmacyclics; MAP: honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, and Takeda. He serves on DSMBs for Servier

and Medigene, and the scientific advisory boards of MolMed and NexImmune. Research support for clinical trials from Incyte, Kite (Gilead) and Miltenyi Biotec.

Contributions: RJL and MAP designed the study and wrote the manuscript. RJL, SML, SMD, and MAP analyzed the data. RJL, MSP, HTC, YB, JDR, TAE, MAM, MLS, and CAB contributed essential data management. BK and SJK performed geriatric assessment. All remaining authors enrolled patients and contributed data to the study. Every author critically appraised and approved the submitted manuscript.

Funding: this research was supported in part by the National Institutes of Health/National Cancer Institute's Cancer Center Support Grant P30 CA008748 and the Program Project Grant P01 CA023766. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. RJL acknowledges research support from the Elsa U. Pardee Foundation for Cancer Research, New York State Empire Clinical Research Investigator Program (ECRIP), and Parker Institute for Cancer Immunotherapy (PICI) at MSK. This work was presented in part at the 61st American Society of Hematology Annual Meeting & Exposition from December 6-10, 2019, Orlando, FL, USA.

References

1. Soubeyran P-L, Cordoba R. Approaches for vulnerable and frail older patients with diffuse large B-cell lymphomas. Curr Opin Oncol. 2019;31(5):369-373.
2. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.
3. Hunter BD, Rogalski M, Jacobson CA. Chimeric antigen receptor T-cell therapy for the treatment of aggressive B-cell non-Hodgkin lymphomas: efficacy, toxicity, and comparative chimeric antigen receptor products. Expert Opin Biol Ther. 2019;19(11):1157-1164.
4. Lin RJ, Elko TA, Devlin SM, et al. Impact of geriatric vulnerabilities on allogeneic hematopoietic cell transplantation outcomes in older patients with hematologic malignancies. Bone Marrow Transplant. 2020;55(1):157-164.
5. Perales M-A, Bonafede M, Cai Q, et al. Real-world economic burden associated with transplantation-related complications. Biol Blood Marrow Transplant. 2017;23(10):1788-1794.
6. Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019; 25(4):625-638.
7. Pennisi M, Jain T, Santomasso BD, et al. Comparing CAR T-cells toxicity grading systems: application of ASTCT grading system and implications for management. Blood Adv. 2020;4(4):676-686.
8. Nastoupil LJ, Jain MD, Spiegel JY, et al. Axicabtagene ciloleucel (Axi-Cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. Blood. 2018;132(Suppl 1):91.
9. Jacobson CA, Hunter B, Armand P, et al. Axicabtagene ciloleucel in the real world: outcomes and predictors of response, resistance, and toxicity. Blood. 2018;132(Suppl 1):92.
10. Smith SD, Reddy P, Sokolova A, et al. Eligibility for CAR T-cell therapy: an analysis of selection criteria and survival outcomes in chemorefractory DLBCL. Am J Hematol. 2019;94(4):E117-E116.
11. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
12. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
13. Bowcock SJ, Fontana V, Patrick HE. Very poor performance status elderly patients with aggressive B cell lymphomas can benefit from intensive chemotherapy. Br J Haematol. 2012;157(3):391-393.
14. Spina M, Merli F, Puccini B, et al. The elderly project by the Fondazione Italiana Linfomi: a prospective comprehensive geriatric assessment (CGA) of 1353 elderly patients with diffuse large B-cell lymphoma. In: Hematologic Oncology, 2019:p S2. Published by John Wiley & Sons, Ltd.
15. Jain T, Bar M, Kansagra AJ, et al. Use of chimeric antigen receptor T cell therapy in clinical practice for relapsed/refractory aggressive B cell non-Hodgkin lymphoma: an expert panel opinion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(12):2305-2321.