Review Article

Transplant and chimeric antigen receptor T-cell therapies in elderly patients with lymphoma, a narrative review

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Background and Objective: Commonly used cellular therapies in lymphomas include stem cell transplantation, both autologous and allogeneic, as well as chimeric antigen receptor T-cell (CAR-T) cell therapies. Many patients diagnosed with lymphoma are older, with a wide range of function and comorbidities. The use of transplantation has been described in patients in their 60s and 70s with success. CAR-T therapies are increasingly being explored in older patients as well.

Methods: We performed a literature review to describe the outcomes of older individuals undergoing cellular therapies.

Key Content and Findings: Autologous transplantation has been extensively described in patients in their 60s. It has also been described in several smaller series in patients over the age of 70 years. Transplant related mortality (TRM) can be as low as 5% at 1 year in selected patients in their 70s. The use of allogeneic transplantation (alloHSCT) for lymphoma has been less extensively described in elderly patients, but rates of TRM of 11–25% have been described in several series. CAR-T cell therapy can be used in selected patients who would otherwise not be eligible for curative intent therapies with transplantation. Rates of TRM with CAR-T therapies are frequently less than 5% in elderly patients. There does not appear to be an upper age limit to CAR-T therapies. Geriatric assessment and other simplified risk scores may help to improve outcomes with elderly patients undergoing cellular therapy.

Conclusions: Cellular therapy is feasible in elderly patients with lymphoma with acceptable TRM rates.

Keywords: Elderly; stem cell transplant; chimeric antigen receptor T-cell (CAR-T)

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Introduction

Cellular therapies have long been an important tool for the treatment of lymphomas, especially in the relapsed and refractory settings. The use of stem cell transplant, both autologous and allogeneic, has been increasingly used in older patients, and now is commonly used in fit patients in their late 60s and 70s (1). The development and approval of chimeric antigen receptor T-cell (CAR-T) therapies has provided a new tool in which patients can access potentially curative therapies in lymphomas that may have not responded to, are ineligible for, or in-lieu of transplantation. CAR-T therapies have also demonstrated a toxicity profile that can often be tolerated by older patients who may not be candidates for autologous or allogeneic stem cell transplantation. Here we review the rapidly evolving field of cellular therapies as they are applied to older patients with lymphomas. Here, we present the

following article in accordance with the Narrative Review reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-22-7/rc).

Methods

A literature review was performed in PubMed using both general search, as well as MeSH terms pertinent to cellular therapies, stem cell transplantation, lymphoma, and elderly populations. The timeframe of the search focused on manuscripts published between 1/1/2020 and 6/1/2022. The search was supplemented by review of abstracts submitted to major national conferences such as ASH and ASCO.

Autologous stem cell transplantation (ASCT)

The role of ASCT in elderly patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (nHL) is rapidly changing with the development of CAR-T therapies (2-6). While more effective salvage and novel cellular therapies are replacing the role of ASCT in B-cell nHL and HL, there has not been the same therapeutic advances in T-cell lymphomas, where autologous transplant continues to be commonly used for consolidative purposes (7). Therefore, while ASCT use will be less common for lymphomas, there will persist a need for select populations, which will include older patients, to undergo this process.

Feasibility of ASCT in the elderly

Multiple retrospective series have examined and demonstrated the feasibility of ASCT in elderly patients, while noting that increased toxicity and transplant related mortality (TRM) can also be seen (*Table 1*). Over the past 2 decades, an improvement in transplant related outcomes has been seen in parallel with increasing age at which a patient is considered "elderly"—previously 60 years, to now commonly defining this population as those older than 70 years (8-13).

One of the larger analyses of 60+ years old patients was a Canadian cohort enrolled on Canadian Cancer Trials Group (CCTG) Ly.12, a trial designed to compare salvage regimens [DHAP (dexamethasone, cytarabine, cisplatin) *vs.* GDP (gemcitabine, dexamethasone, cisplatin)] prior to autologous transplant consolidation. A post-hoc analysis compared outcomes in patients older and younger than 60 years (11). Of the 177 patients in the 60+ cohort, only 30 of those were older than 65 years, with 74 years being the age of the oldest patient. The 100-day post-ASCT mortality was 8.06% in patients over 60 years old and 1.85% in patients 60 years and younger. Notably, this did not translate in to a difference in OS at 4 years. Supportive care for older patients undergoing transplant may have improved since this trial finished enrolling in 2011, with resultant decrease in non-relapse mortality (NRM) over the last decade. However, improvement in non-transplant salvage and cellular therapies, especially for B-cell lymphomas, also will decrease the need for ASCT.

Fewer studies have evaluated ASCT for patients in their 70s (8,10,13-15). Massachusetts General Hospital/Dana Farber Cancer Institute (MGH/DFCI) recently defined outcomes for patients specifically in their 70s undergoing ASCT for lymphoma (8). This analysis included 107 patients with a median age of 72 years (range, 70–79 years) transplanted between 2000 and 2016. Twenty-four of the 107 patients were 75 years or older, and 46% of patients had a Hematopoietic cell transplantation specific comorbidity index (HCT-CI) score of 3 or higher. The majority of patients were conditioned with CBV (cyclophosphamide, BCNU, VP-16) (44%), BEAM (BCNU, etoposide, cytarabine, melphalan) (31%), or Bu/Cy (busulfan, cyclophosphamide) (24%). Importantly, the non-relapse mortality in this study was only 2% at 100 days and 5% at 1-year, supporting the feasibility of transplant in this population. Of the three deaths within the first 100 days, only one was due to multi-organ failure/sepsis, with the other two being due to disease progression and therapy related acute myeloid leukemia (AML). Disease relapse accounted for the majority (31 of 43) of cases of late mortality in this population, and transplantation with active disease was associated with worse progression free survival (PFS) and higher relapse risk. This clearly demonstrates the feasibility of transplant in patients that are in their 70s, as well as the need for disease control before transplant.

Another large series of 20 French transplant centers described outcomes in 81 patients who underwent ASCT for nHL between 1995 and 2009 (10). Median age was 72 years with the oldest patient being 80 years. The majority of patients were conditioned with BEAM (75%) or melphalan alone (17%). Seventy-three percent of patients had a low HCT-CI score. The non-relapse mortality was 5.4% at 100 days 8.5% at 1-year. Notably, the four early deaths occurred in patients between ages 70–72 years with and HCT-CI of 0 in three patients and 1 in the fourth patient. All patients who experienced NRM received multiagent conditioning (BEAM or TT/Bu/Cy). The main cause of death was relapse (60% of deaths).

Table 1 Selected series describing autologous and allogeneic transplantation in elderly lymphoma patients

Reference	Median age (years)	Age range (years)	Number of patients	Lymphoma types	TRM/NRM	PFS	OS
Autologous transplantation							
Jantunen *et al.*, 2008; EBMT registry retrospective series	63	60–74	463	DLBCL	4% at 100 days; 9% at 1 year	51% at 3 years	60% at 3 years
Andorsky *et al.*, 2010; UCLA Retrospective Series	72	70–78	17	All lymphomas	18% at 100 days; 35% at 1 year	Not reported	50% at 2.6 years
Elstrom *et al.*, 2011; Cornell retrospective series	71	69–86	69+ years: 21; 75+ years: 5	All lymphomas	19% at 100 days	50% at 8 months	50% at 18 months
Chihara *et al.*, 2014; Japanese JSHCT retrospective series	64	60–78	60+ years: 271; 70+ years: 39	DLBCL	4% at 100 days; 6% at 1 year	48% at 2 years	58% at 2 years
Hermet *et al.*, 2015; French SFGM-TC registry data	72	70–80	81	nHL	5% at 100 days; 9% at 1 year	50% at 21 months	50% at 43 months
Davison *et al.*, 2017; CCTG LY.12 subgroup analysis	64	60–74	60+ years: 177; 65+ years: 30	R/R aggressive lymphoma	8% at 100 days; (60+ years cohort)	31% at 4 years (EFS)	36% at 4 years
Sun *et al.*, 2018; DFCI/ MGH retrospective series	72	70–79	70+ years: 107; 75+ years: 24	All lymphomas	2% at 100 days; 5% at 1 year	58% at 2 years	65% at 2 years
Dahi *et al.*, 2021; MSKCC retrospective series	66	60–77	60+ years: 346; 70+ years: 67	All lymphomas	3% at 1 year; (70+ years old cohort)	50% at 8 years	50% at 10 years
Allogeneic transplantation							
Kasamon *et al.*, 2015; JHU Haplo PTCy in older adults	61	50–75	50+ years: 271; 60+ years: 129; 70+ years: 27	Any indication for alloHSCT (58% were for lymphoma)	At 100 d/1 year. 60–69 years old: 8%/14%; 70–75 years old: 7%/11%	60+ years old nHL cohort: 53% at 1 year; 39% at 3 years	60+ years old nHL cohort: 66% at 1 year; 49% at 3 years
Muffly *et al.*, 2017; 70+ CIBMTR analysis	72	70–84	1,106	Any indication for alloHSCT (10% were for nHL)	25% at 1 year	No lymphoma subset described	No lymphoma subset described
Shah *et al.*, 2018; Medicare-age CIBMTR analysis	68	65–77	446	nHL	7% at 100 days; 18% at 1 year	53% at 1 year	67% at 1 year

TRM, transplant related mortality; NRM, non-relapse mortality; PFS, progression free survival; OS, overall survival; DLBCL, diffuse large B cell lymphoma; nHL, non-Hodgkin's lymphoma; R/R, relapsed/refractory; alloHSCT, allogeneic transplantation.

Memorial Sloan Kettering Cancer Center (MSKCC) described their experience transplanting 67 patients between the age of 70–77 years (median age 72 years old) and compared these to a cohort of patients between 60–69 years old (13). They described low NRM in the older group at 2.99% at both 100 days and 1 year. All patients were conditioned with BEAM and received granulocyte colony stimulating factor (G-CSF) support. Engraftment was the

same in both age groups with neutrophil engraftment at day +10 and platelet engraftment at day +21. Higher rates of grade 3+ cardiovascular toxicity (hypertension, syncope, arrhythmia, and hypotension most common) and skin toxicity were seen in the older patients as compared to the younger cohort. The most common grade 3 toxicities were febrile neutropenia without a source (70% in the older cohort), oral/gastrointestinal (GI) toxicity (58%), cardiovascular toxicity (57%) and infection (34%). Median PFS and overall survival (OS) for the entire cohort were 8.32 and 10.45 years respectively, noting this series included various lymphoma histologies.

As compared to the MGH/DFCI and MSKCC data, the French group showed slightly higher early transplant mortality, noting that the patients in their cohort were transplanted from a slightly earlier era. However, these studies suggest that it is reasonable to quote a risk of early mortality of 5% or less in selected patients in their 70s undergoing autologous transplantation. Importantly, both advanced age as well as chemotherapy exposure are known risk factors for development of myeloid neoplasms. In these series, 3/107 (2.8%) of the MGH/DFCI cohort, 1% of the MSKCC cohort, and 2/81 (2.5%) of the French cohort developed secondary myeloid neoplasms, which is in line with other reported series ranging from 1% at 2 years to 10% at 6 years depending on length of follow-up and conditioning regimens including use of TBI (16). Median time to engraftment was 12 days or less in these series and median hospital stay was 21 days. Use of the HCT-CI score was not predictive of survival in in these three series, although there was a trend towards higher NRM in HCT-CI high risk patients in the MGD/DFCI cohort (HR 3.45, 95% CI: 0.93–12.86, P=0.065).

Changing indications for ASCT

ASCT has been frequently used in various lymphoma histologies including Hodgkin's, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Mantle, peripheral T-cell lymphoma (PTCL) and CNS lymphomas. It is most frequently used for chemo-sensitive disease in lymphoma, and generally is not advised in patients with chemo refractoriness. Historically, ASCT has been a standard of care for R/R DLBCL, early relapsing FL, and as consolidation in mantle cell lymphomas (MCLs). However, the success and approval of CAR-T therapies is rapidly changing the indications for transplant in these diseases. Additional work is being performed investigating the utility of CAR-T cells targeting CD30 in Hodgkin's, while successfully targeting PTCL has been more difficult (NCT04502446) (17). Improvement in salvage therapies has been significant as well in the last decade, de-emphasizing the need for curative therapy for long-term disease control in some patients. Similar trends are seen with development of novel regimens for initial treatment of elderly patients to increase frontline cure rate (18,19). These therapeutic improvements must be taken into context when deciding on the need for transplantation in an elderly adult.

Autologous transplantation has long been used in relapsed and refractory Hodgkin's Lymphoma based on improved disease control and survival (20). In patients who have high risk disease characteristics, maintenance therapy with brentuximab vedotin should be considered based on the ATHERA trial, especially if not previously treated with that agent (21). However, improved salvage therapies with brentuximab vedotin as well as immune checkpoint blockade can provide substantial benefit and possibly years of disease control with sequencing of salvage therapies and strategies such as treatment beyond progression with checkpoint inhibitors (22,23). Similarly, therapeutic advances with durable salvage therapies as well as CAR-T therapies and bispecific T-cell engager (BITE) in the future are decreasing the need for autologous transplant in DLBCL and FL (3,24-26).

While salvage therapies, including CAR-T, have dramatically improved the prognosis of MCL, they have not replaced the current role of ASCT in consolidation to extend the length of the first remission; noting the benefit of ASCT consolidation is based on randomized trial data that is now approaching two decades since initial publication (27). This initial trial from the European MCL network excluded patients over the age of 65 years, and many centers currently use this age as a cutoff of ASCT consolidation in MCL, with few centers extending this procedure to patients over the age of 70 years due to concerns of toxicity outweighing benefit. The current US intergroup trial, EA4151 (NCT03267433), assessing the role of ASCT consolidation in minimal residual disease (MRD)-negative patients also excludes patients over the age of 70 years. Given the lack of data on the benefits of consolidative transplantation of patients in their 70s, along with the improvement of salvage therapies, ASCT consolidation in CR1 should play a limited role in this population. In the rare patient greater than 70 years old being considered for ASCT consolidation, TP53 should first be sequenced, as those with mutated TP53 show no benefit from ASCT consolidation (28).

The area where ASCT in elderly lymphoma patients will likely remain of most utility is in T-cell lymphoma. Long-term survival in the common histologies of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)-negative ALCL is in the 30–50% range with a low number of cures (29). Earlier studies of ASCT in PTCL demonstrated long-term PFS of approximately 45% with OS between 50–60% (30,31). Patients who have $CD30^+$ disease may have improved outcomes with incorporation of brentuximab vedotin based on ECHELON-2 demonstrating 5-year PFS/OS of 51%/70% (32). However, it should be noted that 22% of ECHELON-2 patients underwent a consolidative ASCT and outcomes in the non-ALCL histologies were poorer with 5-year OS 46% in the PTCL-NOS population. In the salvage setting, T-cell lymphomas have not experienced the numerous advances in therapeutics that has been seen in B-cell lymphoma, and ASCT will likely remain a need for this population. The benefits of transplantation in PTCL, especially in high risk disease, continues to be demonstrated—however, whether this benefit extends to patients in their 70s is unknown (33). There should be thorough discussion about the risks and potential benefits of transplantation prior to moving forward with any patient in T-cell lymphoma.

Allogeneic stem cell transplantation

Allogeneic transplantation (alloHSCT) has played a limited role in lymphomas, and much of the data on transplantation in elderly populations is extrapolated from larger datasets in the acute leukemias (*Table 1*). Historically, multiply relapsed B-cell lymphoma would be one indication for alloHSCT, but the development of improved salvage therapies, CAR-T therapies, and BITE therapies are rapidly changing that paradigm (34). alloHSCT was long thought of as the only route to cure in Richter's Transformation of CLL to large cell lymphoma, however there is now experience in using CAR-T in in this setting and that paradigm may change as well, especially for older patients who may be at higher risk of toxicity with alloHSCT (35). alloHSCT may continue to play a role in a limited number of relapsed T-cell lymphoma patients. One pertinent issue that should be noted is the current limitation in access to alloHSCT for elderly lymphoma patients due to regulations by the Centers for Medicare and Medicaid Services in the United States (36).

The advent of reduced intensity conditioning (RIC) and non-myeloablative (NMA) conditioning regimens have greatly decreased toxicity of alloHSCT in the elderly. Similarly, in elderly patients without sibling or NMDP matches, the use of post-transplant cyclophosphamide (PTCy) GVHD prophylaxis has opened the donor pool to allow for other family members (e.g., adult children) to provide a graft source for elderly patients. With these improvements, multiple analyses across hematologic malignancies have demonstrated the feasibility of alloHSCT in selected patients in their 60s and 70s with multiple studies demonstrating a NRM of approximately 30% and long-term survival approaching 50% in lymphoma patients (1,36).

Identification of the optimal conditioning regimen in elderly patients is an important modifiable risk factor in alloHSCT, and myeloablative conditioning (MAC) has been associated with decreased survival in older patients (1). Several analyses have demonstrated that use of the melphalan containing Flu/Mel140 RIC regimen has been associated with increased toxicity. A CIBMTR analysis in DLBCL patients compared various RIC conditioning regimens and found that use of Flu/Bu was associated with a lower NRM risk as compared to Flu/Mel140 (HR 2.33; 95% CI: 1.42–3.82; P=0.001), even when adjusted for comorbidities and age. In this analysis, they also noted that significantly more patients were older than 60 years in the Flu/Bu cohort as compared to the other RIC cohorts (37). This finding was replicated in another analysis comparing several RIC and NMA regimens and found that more intensive RIC conditioning regimens such as Flu/Mel140 are associated with higher NRM and lower OS (38). An analysis looking at conditioning intensity specifically in T-cell lymphoma did not find differences in survival, NRM, nor relapse between MAC and RIC regimens, but notably this analysis did not include patients over the age of 65 years (39). These analyses would support the use of RIC or NMA conditioning in elderly patients, with less intensive regimens such as Flu/Bu or Flu/Cy/TBI preferred over more intensive RIC regimens such Flu/Mel140 in order to mitigate toxicity and NRM.

While calcineurin inhibitor based regimens such as tacrolimus/methotrexate have long been a standard prophylactic therapy for graft-verses-host disease (GVHD) in alloHSCT patients, the use of PTCy has recently become more prevalent, allowing more successful alternative donor transplantation. Elderly patients receiving PTCy GVHD

prophylaxis were described in a series by the Johns Hopkins group, in patients 50–75 years old with 27 patients between the ages of 70–75 years. There was no association between age and NRM nor survival in this series. Three-year PFS in for patients with aggressive nHL was 39% and for indolent or MCL was 37% (40).

alloHSCT is an area where there is significant work in using tools such as comprehensive geriatric assessment (CGA) to further define the fitness of a patient prior to transplant in order to allow for better patient selection and early intervention to improve outcomes, as further described later (41-43). The ongoing Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial 1704 (NCT03992352), the "CHARM" study, will also provide insight into risk factors for TRM in the elderly patient population.

CAR-T therapy

The development and approval of CAR-T cell therapies has provided much needed options for high risk B-cell populations with otherwise poor prognoses (44,45). Initial approval of these therapies was for DLBCL patients after at least two lines of therapy, and did not directly impact use of autologous transplantation as a standard second line therapy. However, recent trials directly comparing CAR-T *vs.* salvage therapy with autologous transplant consolidation have demonstrated the superiority of several CAR-T products in patients who have relapsed within 12 months of first line therapy (46,47). There are additional CAR-T approvals in other disease states such as relapsed FL and MCL (3,48).

All current FDA approved therapies for lymphoma specifically target CD19 expression on B-cells. Other targets such as CD30 are currently under investigation (17). One of the major differences between CAR-T products lies in the costimulatory domain, either CD28 or 4-1BB, that provides a co-activation signal to the CAR-T cell once the cell is engaged to a CD19 expressing B-cell. This second signal via the costimulatory domain important to the activation and expansion of CAR-T cells, but is also thought to be a reason for the differing toxicity profiles of CAR-T products (49). Both axicabtagene ciloleucel ("axi-cel") and brexucabtagene autoleucel ("brexu-cel") contain a CD28 costimulatory domain, while tisagenlecleucel ("tisa-cel") and lisocabtagene maraleucel ("liso-cel") have 4-1BB costimulatory domains. The CD28 costimulated products are generally thought to have more rapid expansion *in vivo*, but may also have higher rates of cytokine release syndrome (CRS) and neurotoxicity, formally called "immune effector cell associated neurotoxicity syndrome" (ICANS). A unique product difference with liso-cel is that the CAR-T cell product is returned to the patient in a defined ratio of independently expanded CD4 and CD8 T-cells with the hypothesis of improved proliferation from CD4/CD8 synergy, although this has been not been definitively proven to result in product superiority in humans (50). There are no RCTs directly comparing products and it is not currently known if any product is more efficacious nor safer than others (51).

Efficacy of CAR-T therapy in elderly patients

It is clear that there are a population of patients who are not candidates for ASCT, but are able to tolerate and benefit from CAR-T therapy. Registrational trials for CAR-T products include patients into their 70s and 80s (2,3,5,48,52). Notably, in the TRANSCEND trial of lisocabtagene maraleucel, 10% of patients were 75 years or older, with the oldest patient age 86 years (2). More recent retrospective analyses further support the treatment of selected patients into their 80s (*Table 1*) (53,54). The efficacy of CAR-T therapies in elderly patients have been most widely described in retrospective collaborations and post-hoc analyses of the large-cell lymphoma population (*Table 2*).

The US CAR-T Consortium reported on patients receiving the CD28 co-stimulated product axi-cel demonstrating that overall response rates as well as progression-free and OS were similar between patients younger and older than 65 years, with an increased rate of complete responses in the older population (71% *vs.* 51%, P<0.01) (53,55). A post-hoc analysis of the registrational trial for axi-cel (ZUMA-1) also suggests that elderly patients experience the same, and possibly higher, efficacy as demonstrated across multiple measures including overall response rate (ORR) (92% *vs.* 81%), complete response (CR) (75% *vs.* 53%), and PFS (13.2 *vs.* 5.6 months) (52). Whether the signal of increased efficacy in older populations is true is not clear at this time. Hypotheses to possible mechanisms of increased efficacy in older patients could include use of less lymphotoxic therapies such as autologous transplantation in older individuals prior to CAR-T lymphopheresis, resulting in a healthier pheresis T-cell product; or differences in T-cell subsets at time of pheresis between younger and older patients.

Table 2 Selected series describing CAR-T therapies in older lymphoma patients

Series	Median age (years)	Age range (years)	Number of patients	Product and costimulatory domain	Lymphoma types	Grade 3+ CRS and grading system	Grade 3+ neurotoxicity and grading system	TRM/NRM	PFS	OS
Sano *et al.*, 2019; Axi-cel in older patients: US CAR-T consortium	Not reported	65 and older	65+: 94 patients	Axi-cel; CD28	R/R LBCL (3rd line or greater)	7%; Lee	35%; CARTOX and CTCAE	2 deaths	50% at 9.2 months	Not assessable
Schuster *et al.*, 2019; JULIET	56	22–76	All: 111 patients; 65+: 25 patients	Tisa-cel; 4-1BB	R/R LBCL (3rd line or greater)	22%; Penn	12%; CTCAE 4.03	0%	Not reported	50% at 12 months (infused pts only)
Neelapu *et al.*, 2020; ZUMA-1 subgroup analysis of elderly patients	69	65–76	27 patients; (65+ subgroup only)	Axi-cel; CD28	R/R LBCL (3rd line or greater)	7%; Lee	44%; CTCAE 4.03	4%	50% at 13 months	54% at 2 years
Wang *et al.*, 2020; ZUMA-2	65	38–79	All: 68 patients; 65+: 32 patients	Brexu-cel; CD28	R/R MCL	15%; Lee	31%; CTCAE 4.03	0%	61% at 1 year	83% at 1 year
Abramson *et al.*, 2020; TRANSCEND NHL-001	63	54–70	All: 344 patients; 65+: 112 patients; 75+: 18 patients	Liso-cel; 4-1BB	R/R LBCL	2%; Lee	10%; CTCAE 4.03	3%	44% at 1 year	58% at 1 year
Nastoupil *et al.*, 2020; Axi-cel for R/R LBCL: US CAR-T consortium	60	21–83	All: 298 patients; 60+: 154 patients	Axi-cel; CD28	R/R LBCL (3rd line or greater)	7%; Lee and CARTOX	31%; CARTOX and CTCAE	1 patient (HLH)	45% at 1 year	64% at 1 year
Kamdar *et al.*, Blood 2021; TRANSFORM ASH Abstract	60	20–74	92 patients	Liso-cel; 4-1BB	R/R large-cell lymphoma (2nd line)	1%	4%	Not reported; No CRS/ ICANS related deaths	50% at 15 months	OS data not yet mature
Jacobson *et al.*, 2021; ZUMA-5	61	53–68	153 patients; 65+: 34%	Axi-cel; CD28	R/R FL and MZL	7%; Lee	19%; CTCAE 4.03	3%	66% at 18 months	87% at 18 months

Table 2 (*continued*)

Table 2 (*continued*)

Series	Median age (years)	Age range (years)	Number of patients	Product and costimulatory domain	Lymphoma types	Grade 3+ CRS and grading system	Grade 3+ neurotoxicity and grading system	TRM/NRM	PFS	OS
Lin *et al.*, 2021; MSKCC analysis of elderly DLBCL	72	67–86	42 patients	Tisa-cel or Axi-cel	DLBCL	8%; ASTCT	25%; ASTCT	1 death	Not reported	Not reported
Ram *et al.*, 2021; Israeli series in 70+ years old	76	Not reported	41 patients	Tisa-cel and Axi-cel	R/R LBCL (3rd line or greater)	9.8%; ASTCT/EBMT	2.5%; ASTCT/ EBMT	0% at 3 months	39% at 6 months	74% at 6 months
Wang *et al.*, 2021; Brexu-cel for R/R/ MCL: US CAR-T consortium	67	34–89	107 patients	Brexu-cel; CD28	R/R MCL	8%	33%	3 deaths through day +30; 6 deaths through 3 months	81% at 3 months	82% at 3 months
Iacoboni *et al.*, 2022; European Real-World Brexu-cel experience in MCL	67	47–79	33	Brexu-cel; CD28	R/R MCL	3%; ASTCT	36%; ASTCT	15%	51% at 1 year	61% at 1 year
Locke *et al.*, 2022; ZUMA-7	58	21–80	All: 180 patients; 65+: 51 patients	Axi-cel; CD28	R/R large-cell lymphoma (2nd line)	6%; Lee	21%; CTCAE 4.03	4% fatal AEs	46% at 2 years	61% at 2 years

CAR-T, chimeric antigen receptor T-cell; R/R, relapsed/refractory; LBCL, large B-cell lymphoma; DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; CRS, cytokine release syndrome; ASTCT, American Society for Transplant and Cellular Therapy; EBMT, European Society for Blood and Marrow Transplantation; CTCAE, Common Terminology Criteria for Adverse Events; TRM, transplant related mortality; NRM, non-relapse mortality; PFS, progression free survival; OS, overall survival; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; AEs, adverse events.

An analysis from Israel of patients receiving axi-cel or tisa-cel compared a cohort of patients over the age of 70 years to a matched younger cohort (56). This analysis demonstrated no difference in the ORR between the younger and older patients with no statistical difference in the median PFS between groups, although the PFS in the younger group was numerically higher at 54% compared to 32% in the elderly at 12 months. Median OS was not reached for either group. It is notable that in this study, the complete response rate was similar to the tisa-cel registrational JULIET trial, likely due to the fact that there was a higher rate of tisa-cel use in this analysis. Also of note, high LDH prior to CAR-T was associated with lower chance of CR in this analysis. This analysis also was unique in that correlative studies demonstrated that older patients did not have higher rates of T-cell exhaustion markers in the pheresis product and there was similar CAR-T expansion at day +7 after infusion.

There has been less analysis specifically looking at older MCL patients receiving CAR-T, but given the higher incidence of MCL in older patients, trials naturally enrolled an older population. The median age was 65 years (range, 38–79 years) in the ZUMA-2 registrational trial of brexu-cel for MCL, and the US CAR-T consortium subsequently provided "real-world" experience of 107 patients treated with brexu-cel with a median age of 67 years (range, 34–89 years) (48,54). An analysis from Europe of 33 patients treated with brexu-cel for MCL reported a median age of 67 years (range, 47–79 years) with subgroup analysis demonstrating no impact of age on survival (57). Similarly, there has been less described specifically regarding efficacy of the more recently approved axi-cel in FL, with the ZUMA-5 trial having a median age of 60 years old (range, 53–67 years) in FL patients, making it difficult to draw conclusions in this population (3).

Safety of CAR-T therapy in elderly patients

Safety of CAR-T therapy in elderly patients is a major consideration and a significant driver of patient selection. Multiple studies have demonstrated the safety of CAR-T therapy in patients, even in older patients who may not be candidates for ASCT. Unique toxicities of note in CAR-T patients include CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenias, and hypogammaglobulinemia. There are likely differential toxicity effects that are seen between the different CAR-T products, possibly due to differences in the co-stimulatory domain. While there are no randomized controlled trials comparing CAR-T products, cross trial comparisons suggest that the CD28 costimulated product axi-cel may be associated with higher rates of toxicity (58-60). However, safe use of axi-cel and brexu-cel in elderly patients has been well described, along with the 4-1BB products tisa-cel and liso-cel.

The US Lymphoma CAR-T consortium has provided significant data describing the safety of CAR-T use in elderly populations. In their analysis of 80 patients who were age 65 and older, they described similar rates of CRS, ICU admission, and length of hospitalization to a younger cohort. However, there was a significantly higher rate of neurotoxicity seen in older patients (78% *vs.* 65%, P=0.08) (55). Similar results were seen in the post-hoc analysis of the ZUMA-1 trial of axi-cel where the older group did not experience more high grade cytopenias, infections, nor CRS; but the older group did experience more high grade neurologic events (44% *vs.* 28%) (52). The authors expanded on the neurotoxicity describing higher rates of encephalopathy (30% *vs.* 21%), agitation (11% *vs.* 2%), and delirium (11% *vs.* 0%) in older patients. This was confirmed again in an analysis by the US Food and Drug Administration which included patients up to the age of 76, with 24% of them over the age of 65. Again, while similar rates of CRS were seen between age groups, older patients did experience more high grade delirium (12% *vs.* 2%) and encephalopathy (35% *vs.* 16%) (61). Other analyses attempted to look at age associated comorbidities and functional status to see if they can predict risk of toxicity with CAR-T therapy. One analysis that compared 24 patients between the age of 67 to 86 years old to a 25-patient cohort <65 years did not identify statistically significant differences between PFS/OS with respect to age, functional limitation, cognitive impairment, nor comorbidity burden (62).

In contrast to previous analyses, another analysis of 298 patients by the US Lymphoma CAR-T Consortium demonstrated that age itself is not a risk factor for neurotoxicity, but that higher tumor burden is associated with increased neurotoxicity, theorizing this is due to greater expansion of T-cells from higher disease burden (53). Given the lack of specific biomarkers for CAR-T associated ICANS, differentiating the higher rates of neurologic events as caused by CAR-T therapy *vs.* general hospital associated delirium is difficult, and presumably some hospitalization associated delirium commonly seen in older patients could be mischaracterized as low-grade ICANS.

In spite of concerns of increased ICANS in older patients, treatment of patients in their 70s with CAR-T

therapy is not uncommon, and multiple studies demonstrate the use of CAR-T therapy in selected patients in their 80s. With improved ability to predict and manage toxicities, the upper age limit of CAR-T therapies is expected to significantly exceed that of autologous and alloHSCT.

Improving outcomes in elderly patients undergoing cellular therapy

Outcomes of older patients undergoing cellular therapies can be improved in several ways. Appropriate patient selection and identification of specific vulnerabilities is an important first step in not only maximizing outcome in patients who undergo cellular therapy, but also in ensuring that patients are not excluded from cellular therapies based on age alone. In elderly patients who are selected to undergo cellular therapy for lymphoma, age-appropriate interventions can be applied to further optimize outcomes.

Patient identification and selection is a critical early step in optimizing outcomes. A specific age should not be the sole determinate of cellular therapy eligibility or not. Use of physiologic or functional age and general health often requires a systematic approach, but can inform cellular therapy candidacy and improve patients outcomes in the elderly (63). There is not a single tool that can adequately assess this in all patients across various cellular therapy modalities. The HCT-CI was initially described in 2005 as a simple tool that could be used to predict non-relapse mortality and survival in patients undergoing alloHSCT (64). However, the median age of patients used to develop this tool was 45 years old (range, 1–73 years). An age-adjusted HCT-CI score was subsequently developed and validated that gave an additional comorbidity "point" for any patient over the age of 40 years old (65). Both the HCT-CI and age-adjusted HCT-CI were developed and validated in patients undergoing HLA-matched alloHSCT prior to 2006. Validation of the HCT-CI score in the broader autologous transplantation setting was demonstrated by Sorror *et al.*, but several analyses have not been able to demonstrate utility of this score in elderly patients (8,10,14,66). HCT-CI has not been found to be a significant predictor of survival in patients undergoing CAR-T, however other scores such as the Cumulative Illness Rating Scale (CIRS) may provide some insight (67). The CIRS is a quantitative scoring system to characterize the severity of impairment in multiple organ systems (68). Elevated CIRS score has been associated with lower survival, with severe dysfunction or specific involvement of the respiratory tract, upper GI tract, liver and kidneys being associated with higher risk (35,69).

One reason for the failure of calculated comorbidity scores in predicting outcomes in elderly cellular therapy patients may be their inability to quantify functional status. Patient falls is one example of a predictor strongly associated with NRM and OS in older patients, yet it is not captured by comorbidity scores such as the HCT-CI (14). This is one example that emphasizes the need to take into account functional limitations in addition to traditionally defined comorbidities when evaluating patients for cellular therapies (70). There are multiple tools to assess various domains of function, nutrition, cognitive ability, and social support in older individuals. Use of these studies and tools has been best described in patients undergoing alloHSCT (71,72). In the autologous setting, these tools have been studied mostly in myeloma patients, with less data in lymphoma patients who may undergo more intensive myeloablative regimens such as BEAM (73). Using geriatric assessment to identify specific patient vulnerabilities can then help to modify those vulnerabilities to optimize patient outcomes.

Specific functional tests that can be performed include patient reported instrumental activities of daily living (IADL) and the timed-up-and-go (TUG) test to measure functional status, the mini mental status exam (MMSE) or Blessed Orientation-Memory-Concentration (BOMC) test to measure cognitive status, reported weight loss and albumin to measure nutritional status, and the MOS Social Support Survey to measure social support. These tests and domains have been evaluated in series and found to be predictive of survival, hospital readmission, length of stay—and have been extensively reviewed elsewhere (70-74). In centers with available resources, full CGA may be beneficial.

Based on vulnerabilities and comorbidities identified using the above tools, targeted interventions can be performed in order to maximize outcomes in patients undergoing cellular therapy. Appropriate engagement of other specialties (e.g., endocrinology in patients with diabetes, or pulmonology in patients with lung dysfunction) to optimize comorbidities prior to treatment is important. In patients with physical and functional limitations, several studies have demonstrated the ability of exercise programs to optimize transplant outcomes, and patients should be evaluated by physical and occupational therapy services both before and during the therapy period (75,76). Additionally, caregiver involvement, social work evaluation, delirium

precautions, medication assessment and optimization, dietary/supplement recommendations from nutrition, fall assessment with walker assistance and oral care with pre therapy dental optimization are all measures that may optimize outcomes (77,78).

Appropriately choosing cellular therapy characteristics and supportive care are other considerations during the planning phase of therapy. This can include use of planned G-CSF support, use of less toxic salvage regimens prior to autologous transplant (e.g., GDP instead of DHAP) to maximize patient fitness, and ensuring appropriate cell doses prior to transplant {e.g., [3–5]×10^6 $CD34^+$ cells/kg}. In patients undergoing CAR-T, minimization of lymphotoxic therapies (e.g., bendamustine) immediately prior to T-cell collection may be beneficial to ensure a healthy T-cell pheresis product. Additionally, adequate disease control prior to stem cell transplantation is needed decrease relapse risk (8,9).

There are also some unique considerations that may help optimize CAR-T therapy in older populations. Product selection should be considered, as analyses suggest that the toxicity profile of 4-1BB co-stimulated products may be less than CD28 co-stimulated products, noting this is a controversial and not proven in a randomized fashion (58,79). However, quicker manufacturing slot availability and product turnaround times may negate this in some situations. Bridging therapy to debulk disease prior to CAR-T infusion may help optimize response and decrease toxicity, with radiation bridging shown to be less immunosuppressive than cytotoxic bridging while remaining efficacious (56,80). The ZUMA-1 trial investigated the use of prophylactic dexamethasone at a dose of 10mg daily over 3 days in 40 patients undergoing axi-cel therapy for DLBCL, and demonstrated low rates of severe neurotoxicity (13% Grade 3+) with no severe CRS without compromising efficacy (81). Conversely, there are concerns about use of prophylactic tocilizumab due to a paradoxical increase in neurotoxicity based on data from Cohort 3 of the ZUMA-1 trial. This data may support use of prophylactic dexamethasone when using CD28 co-stimulated axi-cel in older patients, and could potentially be extrapolated to other 4-1BB costimulated products—noting the presumed benefit is based on a small number of patients in Cohort 6 of the ZUMA-1 trial. Finally, support of the depleted humoral immunity in older patients should include immunoglobulin repletion, consideration of revaccination, and use of products such as tixagevimab + cilgavimab (Evusheld) for COVID19 prevention.

Conclusions and future directions

Cellular therapies such as stem cell transplantation and CAR-T therapies are important modalities for disease control and potential cure in lymphomas. However, they do have increased risks and unique toxicities compared to non-cellular therapies. Balancing these risks and benefits is even more difficult in older patients who may have impaired physiologic reserve. In spite of these difficulties, studies have demonstrated the benefit of these therapies in older patients and the ability to mitigate risk in many circumstances. There has been extensive work in development of assessment tools and their appropriate use in characterizing geriatric vulnerabilities and syndromes in patients who may be candidates for cellular therapies. Incorporation of these tools and data into the day-to-day practice by centers using cellular therapies has the potential to further improve outcomes for older patients in this setting.

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Footnote

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