Cellular therapy in lymphoma

Anna Sureda[1], Pieternella J. Lugtenburg[2], Marie José Kersten[3], Marion Subklewe[4,5], Anne Spanjaart[3], Nirali N Shah[6], Lucila N Kerbauy[7], Clarie Roddie[8], Elise R. A. Pennings[3], Carolina Mahuad[9], Michelle Poon[10], Candice L Hendricks[11,12], Manali Kamdar[13], Caron Jacobson[14,*]

[1]Clinical Hematology Department, Institut Catala d'Oncologia – Hospitalet, Institut d'Investigatcions Biomediques de Bellvitge (IDIBELL), Universitat de Barcelona,
Barcelona, Spain
[2]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands
[3]Department of Hematology, Amsterdam Universitair Medische Centra, Amsterdam, The Netherlands
[4]Department of Medicine III, University Hospital, LMU, Munich, Germany
[5]Laboratory for Translational Cancer Immunology, LMU Gene Center, Munich, Germany
[6]Pediatric Oncology Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI), NIH, Bethesda, Maryland, USA
[7]Departments of Stem Cell Transplantation and Hemotherapy/Cellular Therapy, Hospital Israelita Albert Einstein, Sao Paolo, Brazil
[8]Research Department of Haematology, Cancer Institute, University College London, London, UK
[9]Hematology Service, Department of Internal Medicine, Deutsches Hospital, Buenos Aires, Argentina
[10]Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore
[11]Institute for Cellular and Molecular Medicine, Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[12]SAMRC Extramural Unit for Stem Cell Research and Therapy, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[13]University of Colorado, Aurora, Colorado, USA
[14]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

*Correspondence
Caron Jacobson, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA.
Email: caron_jacobson@dfci.harvard.edu

ABSTRACT

CD19-directed chimeric antigen receptor (CAR) T-cell therapy has had a dramatic impact on the natural history and survival of patients with high-risk B-cell non-Hodgkin lymphoma. Accompanying this success has been the development of new fields of medicine and investigation into toxicity risks and mitigation therapies, mechanisms of resistance and the development of novel and next generation products and strategies in order to address relapse, and issues related to global access and health care economics. This article is a survey of each of these areas as it pertains to the rapidly evolving field of CAR T-cell therapy, written by an International community of lymphoma experts, who also happen to be women.

KEYWORDS: CAR T-cells, lymphoma

1 INTRODUCTION

CD19-directed chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of both high-risk B-cell lymphomas and B-cell lymphomas that have proven to be resistant to chemoimmunotherapy and other lymphoma therapies. Chimeric antigen receptor T-cells induce high rates of durable remissions in patients who might otherwise have been considered for end-of-life care, far outpacing other available therapies in each approved and trialed indication. Despite remarkable success, response is not guaranteed and remissions

are not permanent for the majority, toxicities can be formidable, and access within a country and across the globe is not universal. Here we outline the approved indications of CAR T-cell therapy in B-cell lymphoma, toxicity considerations and management strategies, mechanisms of resistance and emerging cellular therapy strategies to respond to them, and issues related to access on an international scale. In addition, we also discuss changes in the use of allogeneic hematopoietic stem cell transplantation (allo-HCT) as the first cellular therapy strategy introduced in the treatment of patients with relapsed or refractory lymphomas after the advent of CART cells.

2 CAR IN LBCL

Chimeric antigen receptor T-cell therapy has changed the treatment landscape for many patients with relapsed or refractory aggressive B-cell lymphomas. The pivotal phase 2 prospective studies ZUMA-1 (axicabtagene ciloleucel),[1] JULIET (tisagenlecleucel)[2] and TRANSCEND (lisocabtagene maraleucel)[3] enrolled heavily pretreated patients who relapsed after or were refractory to at least two prior lines of standard therapy. Overall response rate (ORR) (52%–74%) and complete remission rate (CRR) (40%–54%) were comparable across age and tumor histology subgroups. Between 35% and 45% of the refractory patients in these studies were disease free 3–5 years after infusion. Several real-world analyses of the use of commercial CAR T-cell products have already been published.[4-9] Real-world treated patients are less refined than those in prospective studies, but clinical results are similar in terms of ORR (59%–84%), CRR (32%–65%) and survival. Data from pivotal studies as well as real-world analyses demonstrate the existence of clinical and biological prognostic factors that impact the long-term survival; although there is not a clear-cut upper age limit, co-morbidities associated to age need to be taken into consideration in the decision-making process. Elevated LDH and CRP, high tumor burden as well as an inadequate performance status are associated to a poorer outcome; obtaining an early complete metabolic is associated with a better prognosis. Chimeric antigen receptor T-cells have also moved to the second line landscape in those patients with primary refractory disease or early relapse after first line therapy thanks to the results of 2 prospective randomized clinical trials: ZUMA-7 (axicabtagene)[10] and TRANSFORM (lisocabtagene maraleucel).[11] Both of them demonstrated that autologous CAR T-cells were able to provide higher ORR and CRR, a better event free survival and improved patient reported outcomes compared with salvage chemotherapy, and if chemoresponsive, autologous stem cell transplantation with a toxicity profile similar to the one observed in later lines of treatment.

On the heels of the success of CAR T-cell therapy, bispecific antibodies (BsAbs) have been developed and clinical trials suggest that they too have formidable efficacy that is superior to other non-CAR T-cell historical treatment options. BsAbs are antibody molecules in which one arm binds to an antigen on the tumor cell and the other arm targets an immune effector cell. Mosunetuzumab,[12] epcoritamab[1, 3] glofitamab[13] and odronextamab[14] target CD20 on the lymphoma cell and CD3 on T cells. These BsAbs have demonstrated very promising efficacy in phase 1-2 studies in heavily pretreated patients with aggressive lymphomas, including in patients relapsing after CAR-T therapy.[1-3] Response rates for BsAbs in patients with aggressive B-NHL range from 36% to 63%, with CR rates of 19%–39%. Follow-up of the studies is still short. Side effects include cytokine release syndrome (CRS) and ICANs, but at much lower frequencies and severity than is reported for CAR T-cells. Longer follow-up is needed to confirm the durability of the complete responses and to see whether cures can be achieved. If approved for aggressive B-cell lymphomas, these BsAbs will offer an off-the-shelf effective immunotherapy with a manageable safety profile, and how they will compete, and be sequenced, with CAR T-cells remains to be determined.

As a consequence of the compelling results of autologous CD19 CART cells, the number of allogeneic transplants has fallen significantly in recent years as shown by both the CIBMTR

and EBMT registries. Allogeneic transplantation is a curative strategy in these patients; however, the need for the patient to be in CR, the high morbidity and mortality associated with the procedure, and the impact that graft-versus-host disease and other associated complications have on patients' quality of life represent significant obstacles to its use today. At present, it is considered a potential salvage strategy of choice in patients who relapse or progress after CART cell therapy; outcomes are best in those patients receiving an allogeneic transplant for late relapse after CART cell therapy.[15]

3 CAR IN MANTLE CELL LYMPHOMA

Mantle cell lymphoma, MCL is a rare subtype of B-cell lymphoma, predominantly seen in elderly, male patients. Clinically it is characterized by frequent leukemic disease and also a predilection for the gastrointestinal tract. Although long-term remissions can be obtained using immunochemotherapy with or without high dose chemotherapy and rituximab maintenance,[16, 17] the disease is considered incurable. CD19 CAR T-cell therapy with brexucabtagene ciloleucel has been shown to be highly effective in a BTK resistant and/or intolerant population in a pivotal phase II trial in which 68 out of 74 enrolled patients with R/R MCL were infused.[18] The ORR in infused patients was 93% (95% CI, 84–98) and 67% (95% CI, 53–78) had a complete response. Cytopenias, CRS (15% ≥grade 3) and neurologic toxicity (NT) (31% ≥grade 3), were the most frequent side effects. At an updated median follow-up of 35.6 months, medians for duration of response, progression-free survival, and overall survival were 28.2 months (95% CI, 13.5–47.1), 25.8 months (95% CI, 9.6–47.6), and 46.6 months (95% CI, 24.9 to not estimable), respectively.[19] Late relapses (>12 months) did occur. In a subset analysis of MCL patients treated with lisocabtagene maraleucel in the TRANSCEND study, the ORR in 32 patients was 84% with 59% CR, with ≥grade ≥3 CRS and/or grade ≥3 NE in only 1 and 3 patients respectively (Palomba et al., ASH 2020, a10).

Real world data on the use of brexucabtagene ciloleucel in patients with relapsed MCL replicate data regarding efficacy although with a significantly lower number of patients and a short follow up but raise some concerns regarding an increased toxicity profile.[20]

As described for patients with relapsed or refractory diffuse large B cell lymphoma ,DLBCL, the use of CART cells rather than allogeneic transplantation is also recommended for relapsed MCL after BTK-I's.[21] Allotransplant can be a treatment option if CAR T-cell therapy has failed or is not feasible.

4 CAR IN INHL

CD19 CAR T-cell therapy was successful in a small number of follicular lymphoma (FL) patients on the first-in-human studies, and some of these patients remain in remission at 10-year follow-up. The ZUMA-5 and ELARA trials tested axicabtagene ciloleucel and tisagenlecleucel, respectively, in patients with r/r FL in the ≥3rd line; ZUMA-5 also included an experimental cohort of patients with marginal zone lymphoma (MZL) after 2+ prior lines of therapy.[22, 23] Both studies demonstrated a very high ORR and CR rate with impressive durability even in high-risk patients like those with POD24; median PFS was 40.2 m on ZUMA-5 and had not been reached on ELARA at 2-years. Compared to matched historical controls (SCHOLAR-5 and RECORD-FL studies), there were statistically significant improvements in ORR/CR, PFS and OS.[24, 25] Efficacy outcomes for the 24 patients with MZL on ZUMA-5 were also quite favorable. Toxicities of CRS and NT amongst FL were more favorable compared with these products in large B-cell lymphoma, but still occurred. This becomes important with the approvals of CD20 BsAbs in FL, which have a high degree of activity with a modestly improved toxicity profile, but with an overall shorter mPFS and with repeated and/or indefinite dosing required. Decisions on how to sequence these therapies, then, will likely be patient-specific. It is too early to know whether CAR T-cells can cure a subset of patients with these

historically incurable lymphomas, but long-term remissions from initial trials along with the success of allogeneic transplant in these diseases provides hope for the definitive potential of this therapy in FL.

Allo-HCT has been for many years the only curative strategy for patients with relapsed or refractory FL and it has mostly been offered to young patients with adequate performance status and chemosensitive disease that do have a donor available relapsing after auto-HCT or multiple lines of therapy.[26] Difficulties in selecting the eligible population of patients, the advent of very effective targeted therapies (e.g., CART cells) with a more benign toxicity profile as well as the inherent toxicities associated to the allograft project have also significantly decreased the interest of the scientific community for allo-HCT in this setting.

5 CAR TOXICITIES

Acute CAR T-cell therapy toxicities of CRS and NT (or immune effector cell associated neurologic syndrome [ICANS]) are well documented and reported. Cytokine release syndrome typically occurs within the first 1–5 days following infusion and lasts 3–5 days, mirroring peak CAR T-cell expansion, but onset and severity vary across unique constructs. Onset is generally earlier, and high-grade CRS is more common, with the CD28 CARs like axi-cel and brexu-cel, compared with the 4-1BB CARs like liso-cel and tisa-cel. Immune effector cell associated neurologic syndrome most commonly occurs at the tail end or following CRS and duration is more variable. Again, any grade and high-grade incidence is generally greater with the CD28 CARs compared to the 4-1BB CARs. These toxicities are generally greatest in patients with the largest tumor burden and highest pre-treatment levels of inflammation. In addition to CRS and ICANS, these is increased recognition that some patients may develop delayed onset of hemophagocytic lymphohiostiocytosis (HLH)-like toxicities. This has been newly termed as immune effect cell associated HLH-like syndrome and further studies are needed to understand the incidence, risk factors for and best approaches to treat this emergent toxicity.

While the clinical trials established the incidence and risk of acute CAR T-cell toxicities of CRS and ICANS, real-world evidence has highlighted the importance of hematological toxicity and subsequent infectious complications as additional components of CAR T-cell related immunotoxicity.[27, 28] These less prominently reported side effects are both exceedingly common, substantially contribute to the toxicity burden of CAR T-cell, and drive non-relapse mortality.[29] Cytopenia can persist long after lymphodepleting chemotherapy and resolution of acute CRS. Three different patterns of neutrophil recovery have been observed: the quick recovery type with a median duration on neutropenia (ANC <0.5 G/L) of 5 days, an intermittent recovery type, with a 2nd dip of ANC <1.0 G/L after day 21 and the aplastic phenotype with continuous severe neutropenia of an ANC <0.5 G/L longer than 14 days[28, 30] The intermittent recovery type occurs in >50% of patients and the initial rise in ANC is often due to G-CSF administration. Two retrospective studies in R/R DLBCL, but also in R/R multiple myeloma ,MM patients, have shown that the incidence of higher-grade CRS/ICANS is not increased through early G-CSF application, and importantly, that CAR T-cell expansion is not negatively impacted.[31, 32] Of note, unresponsiveness to G-CSF has also been shown to be associated with an aplastic phenotype and hence, should initiate further diagnostics. The first step in the work-up comprises defining the differential diagnosis, which can include drug-induced cytopenia, vitamin deficiencies, infectious causes, sustained inflammatory stressors, relapse and bone marrow disease. Therapeutically, G-CSF should be continued in patients with prolonged neutropenia and TPO agonists should be considered in patients with prolonged thrombocytopenia. However, data supporting the use of TPO agonists in the CAR T-cell setting are limited and are based on small retrospective reports of very limited patient numbers.[33-35] In patients with an autologous or allogeneic hematopoietic stem cell backup, a boost without prior conditioning has been shown to be safe and feasible. Albeit the current

reports are based on small observational studies, engraftment of autologous stem cell boosts as well as CD34 selected allogeneic stem cell boosts were observed after 9–42 days in the vast majority of cases.[36-38] To identify patients at high risk for prolonged neutropenia a CAR-HEMATOTOX score was developed.[30] The score incorporates factors related to hematopoietic reserve (ANC, hemoglobin, platelet count) and baseline inflammation (CRP, ferritin) and was validated for a primary endpoint of severe neutropenia (ANC <500/µL) greater than 14 days during the first 60 days after CAR T-cell infusion. Importantly, the parameters for the CAR-HEMATOTOX score are determined prior to the start of lymphodepleting chemotherapy, enabling early risk-stratification into a high versus low risk of severe hematotoxicity.[30] Patients with a high-risk CAR-HEMATOTOX score also more frequently develop infectious complications, are hospitalized longer, and exhibit inferior survival outcomes.[29] Differentiating if an episode of fever is due to an infection versus coincident CRS represents a particular challenge and a recent report integrating the Hematotox score and serum inflammatory markers guides risk-adapted decisions on antibiotic use. This might be of particular benefit also in light of recent findings on the deleterious effect of broad-spectrum antibiotics on the diversity of the gut microbiome and the potential role in relation to toxicity and outcome.[39]

6 HEALTH-RELATED QUALITY OF LIFE AFTER CAR T-CELL THERAPY

In most CAR T-cells studies the main endpoints comprise safety, response and survival data. However, in addition it is key to preserve, but preferably improve health-related quality of life (HR-QoL) of patients. Information regarding HR-QoL domains, such as psychosocial-health and symptom burden can only be accessed by asking patients directly, using PRO measures. Longitudinal PRO results are scarce but reported in some landmark trials (Table 1).[40-42] In general they show a similar pattern with an initial decline (only for axi-cel and liso-cel) from baseline to month 1 after infusion in all broad aspects of HR-QoL, followed by clinically meaningful improvements starting at month 2-3 and onwards.[40] This has also been shown in observational studies.[43] Comparative PRO results for CAR T-cells versus standard of care (SoC) are available for the ZUMA-7 and TRANSFORM trials (axi-cel or liso-cel [respectively] vs. Standard of care in 2nd line R/R DLBCL) and show that CAR T-cells results in statistically and clinically meaningful improvements of HR-QoL at day 100 and 150 over SoC.[41, 42] Compared to contemporary autologous/allogeneic stem-cell transplantation cohorts, the decline of HR-QoL at week 2 is less, return to baseline is faster and symptom burden is lower after CAR T-cells.[44] This evidence indicates that CAR T-cell therapy is associated with improved HR-QoL, but more research is needed. Longitudinal HR-QoL results need to be confirmed in the real world. Electronic PRO monitoring of core signs and symptoms might be a valuable option to gain more insight in the patient's experience of the very early phase of CAR T-cells.[45]

TABLE 1. Patient reported outcome assessments in clinical chimeric antigen receptor T-cells trials.[40-42]

Study	Disease	Phase trial	CAR T-cells product	PRO measure	PRO time-points
ZUMA-2	MCL	1-2	Brexu-cel	EQ-5D	Baseline, month 1, 3, 6
ZUMA-3	B-ALL	1-2	Brexu-cel	EQ-5D-5L	Baseline, day 28, month 3,6,9,12
ELIANA	B-ALL	1-2	Tisa-cel	PedsQl	Baseline, day 28, month 3, 6, 9, 12
				EQ-5D	
JULIET	DLBCL	1-2	Tisa-cel	FACT-Lym	Baseline, month 3, 6, 12, 18
				SF-36	
TRANSCEND	LBCL	1-2	Liso-cel	EORTC-QLQ-C30	Baseline, month 1, 2, 3, 6, 12, 18
				EQ5D5L	
KarMMa	MM	1-2	Ide-cel	EORTC-QLQ-C30	Baseline, day 1, month 1,2,3,4,5,9,12,15,18,21,24
				EORTC-QLQ-MY20	
				EQ-5D-5L	
CAR T-cellsitude-1	MM	1-2	Cilta-cel	EORTC-QLQ-C30	Baseline, day 7, 28, 56, 78, and 100, and then every 28 days after infusion
				EQ-5D-5L	
ZUMA-7	LBCL	3	Axi-cel versus SoC	EORTC-QLQ-C30	Baseline, day 50, 100, 150, month 9, 12, 15, 18, 24
				EQ-5D-5L	

Abbreviations: B-ALL, B-acute lymphoblastic leukemia; DLBCL, diffuse large B cell lymphoma; LBCL, large B cell lymphoma; MCL, Mantle cell lymphoma; MM, multiple myeloma; PRO, Patient reported outcomes; SoC, standard of care.

7 CAR RESISTANCE

Mechanisms of resistance limiting the ability to achieve and maintain a durable remission following single-antigen targeted CAR T-cell therapy broadly fall into two main categories: cancer or tumor microenvironment modulation leading to escape from CAR T-cell targeting or CAR T-cell dysfunction, either intrinsic or due to T-cell exhaustion post-infusion, limiting ongoing anti-cancer efficacy.[46] Converging between these two, tumor intrinsic mechanisms and factors related to the microenvironment are actively being explored in their role in conferring resistance to CAR T-cells.

Antigen loss or antigen downregulation account for the primary forms of immune escape from effective CAR T-cell targeting. CD19 loss is the most well studied and can be due to alternative splicing,[47] impacted sequential antigen targeting,[48, 49] and emergence of pre-existing $CD19^{negative}$ isoforms[50] or potentially, as it has been demonstrated in B-cell ALL, $CD19^{negative}$ hematopoietic stem cell precursors,[51] amongst other etiologies. While antigen loss has been predominantly studied in B-cell acute lymphoblastic leukemia, it also causes treatment failure in B-cell lymphoma[52] where the prevalence and incidence of antigen escape/downregulation are potentially underestimated due to the availability of pre- and post-treatment/relapse biopsy sampling. Dual- or multi-antigen targeted constructs or co-infusion strategies (i.e., with CD19 and CD22/CD20) as a combinatorial strategy offers the potential of overcoming the problem of single antigen targeting and immune escape.[52-54] Future efforts will warrant close monitoring of dual-functionality and CAR T-cell persistence of these novel approaches while routinely quantitatively assessing target antigen density.

Beyond antigen loss, tumor intrinsic features, such as BCL-2 alternations in lymphoma which may confer resistance to apoptosis[55] and identification of other complex genomic features through whole-genome sequencing[56] are associated with worse outcomes. Indeed, a better understanding of cancer-specific mechanisms that confer resistance will be critical to modify the treatment approach to optimize CAR T-cell outcomes. High-tumor burden, high-pretreatment inflammatory markers, high levels of circulating myeloid derived suppressor cells, and an interferon-gamma gene expression signature have all been linked to each other and to diminished efficacy of axi-cel in large B cell lymphoma ,LBCL and this has been linked to impaired axi-cel expansion as well an altered T-cell phenotype within the pheresis product and a less effective CAR T-cell product.[57, 58] These features all point towards the impact of the tumor and its microenvironment on the peripheral immune state, thus affecting the quality of T-cells collected and the pharmacokinetics and activity of the CAR T-cells upon reinfusion.

Lastly, regarding CAR T-cell failure, a host of strategies are currently utilized. With a goal to optimize the starting material towards a T-cell phenotype that is more effective in targeting and can maintain longevity without T-cell exhaustion, current approaches incorporate the avoidance of highly intensive chemotherapeutics (e.g., clofarabine-based regimens),[59] performing earlier apheresis in high-risk patients before they receive additional chemotherapy, and modifying CAR T-cell manufacturing strategies to optimize the apheresis product (for example, with CD4/CD8 selection[60] or changing cytokine exposure during ex vivo expansion.[61] Use of 'off the shelf' or allogeneic strategies which serve to use more readily available and less exhausted T-cells from health donors are understudy — with reducing rejection risk and ensuring longevity as key goals.

8 NOVEL AND UPCOMING CAR STRATEGIES

As introduced above, novel strategies are required to overcome the main causes of CD19-CAR-T treatment failure in LBCL, namely antigen escape[62] and CAR-T exhaustion following chronic stimulation in vivo.[63] To mitigate for antigen escape, dual antigen-targeting of CD19 +/− CD22 or CD20 has been tested in several clinical studies in LBCL, but to date has not demonstrated clear superiority over single-antigen approaches.[52, 53, 64] CD79b is also being explored as a CAR-T target by some groups.[65] Current research priorities include robust antigen quantitation platforms as applied to pre-CAR-T lymphoma samples to identify patients at risk of antigen escape,[52, 62] and design of CAR constructs with enhanced cytotoxicity at lower antigen densities.[66, 67] To mitigate for CAR-T exhaustion, myriad strategies to improve T-cell 'fitness' have been tested, from engineered co-stimulation[68] and transcription factor overexpression,[55, 69] to the use of small molecules to skew T-cell memory phenotypes,[70] and rapid CAR-T manufacture methods, some within 24 h and in the absence of T-cell activation.[71]

In parallel with developments in B-cell lymphoma, CAR-T therapy for T-cell lymphoma is gaining traction.[72] Initial concerns regarding CAR-T fratricide (and poor in vivo expansion/persistence) and prolonged T-cell depletion (with attendant risks of serious infective sequelae) have been somewhat allayed by clinical trials of CD7-, CD5- and T-cell receptor B-chain constant region (TRBC1)-targeting CAR-T products showing compelling early promise.[73-75]

Compared to autologous CAR-T products, where manufacture is complex, expensive, bespoke, and time-consuming, allogeneic CAR-T therapy is an attractive alternative. Currently, clinical trials of allogeneic CAR-NK-cells for LBCL use peripheral blood from healthy donors,[76] cord blood[77] and induced pluripotent stem cells.[78] In the clinic, cord blood-derived CAR-NK-cells demonstrate remarkable safety and encouraging efficacy.[77] However, preclinical optimization continues toward improved CAR-NK-cell therapy by increasing NK-cell persistence and cytotoxicity by modulation of co-stimulation, checkpoint inhibition, cytokine armoring and reductions in trogocytosis.[79, 80] In preclinical tumor models, next-generation

CAR-NK-cells showed improvements in cytotoxicity, with a parallel reduction in NK cell exhaustion and fratricide. The result was enhanced antitumor activity.[81]

9 ACCESSIBILITY TO CAR AROUND THE GLOBE

9.1 US

Since 2017, the US Food and Drug administration has approved CD19 targeted CAR-T cell therapy in nearly eight indications for relapsed lymphomas. Although life altering for several patients, several barriers to optimal uptake and effective implementation have thwarted the true impact of this therapy. Some of the common roadblocks range from cellular therapy-specific factors like complex manufacturing, lack of apheresis slots, and out of specification products, to logistical issues of access to a CAR-T site, insurance approval and racial disparity. Financial toxicity and reimbursement challenges remain ongoing hurdles further adding to the complexity around accessibility to novel treatments.

9.2 EU

Healthcare in Europe differs across countries, including healthcare financing, resources and organization. With regards to CAR T-cell access, there currently is a major difference between countries in Europe, ranging from adequate access to no access, neither through participation in a clinical trial nor as SoC. The latter situation is particularly urgent in most countries in Central and Eastern Europe. High costs and logistical complexity are the main barriers impeding widespread implementation of CAR T-cell therapy in Europe.

9.3 LATAM

The LATAM situation regarding cell therapies is quite heterogeneous, just like the access to health care. Among LATAM countries, only Brazil and Argentina have access to CAR T-cells. In Argentina, only in the framework of clinical trials. Some countries are working on local manufacturing of academic products to reduce costs and facilitate access to the general population. The current cost of commercial CARs makes them unaffordable for LATAM. In Argentina, we have broader experience with BsAbs than with CAR T-cells, also in the framework of clinical trials, both for MM and lymphoproliferative neoplasms.

9.4 Asia

With 48 countries within the Asia continent and socioeconomic disparities amongst various countries in the region, this has also led to significant heterogeneity in cell therapy activity and accessibility to the various types of CAR T cell therapy and products.

For commercial CAR T-cell therapy (KYMRIAH and YESCARTA), one or both are available or launching soon in multiple Asian countries including China and Hong Kong, South Korea, Japan, Israel, Singapore, Taiwan, Saudi Arabia. Financial reimbursement for these products also varies, with CAR T-cells being government funded in some countries, covered by private insurances or self-paid by patients in others. In order to increase accessibility, several Asian countries are also working on clinical trials of in-house manufactured academic products for their local population. Of these, China is amongst the forefront in Asia with multiple innovative CAR T-cell products and more than 50 local companies pursuing cell therapy. Regulatory authorities have also actively involved, and specific legislation has been set up to govern practice in the field of cell and gene therapy.

9.5 South Africa

South Africa presently has no CAR T-cell access and will be initiating its first CAR T-cell trial in the latter half of 2023. This trial will inform the introduction of gene therapy regulation. Due to the cost of commercial therapies, the growth in the South African industry will be focused on local manufacturing capacity in an effort to make these therapies more widely accessible.

10 CONCLUSIONS

This special edition of Hematologic Oncology allowed for the collaboration of an international group of cell therapy experts, who also happen to be women, to offer both their shared and unique perspectives on CAR T-cells therapies and other emerging cellular therapies for the treatment of lymphomas. Approvals, CAR T-cell availability, and access to clinical trials may differ across the globe, with each region experiencing their own successes as well as challenges. There is one universal message, however, from this global community: CAR T-cell therapy marks a giant step forward for the treatment of lymphoma patients near and far, and as a new and emerging field, ongoing research collaborations are vital in our efforts to improve efficacy, prevent and treat toxicities, and increase access for all corners of the world.

CONFLICT OF INTEREST STATEMENT

Consulting for Kite/Gilead, Novartis, BMS/Celgene, Instil Bio, ImmPACT Bio, Abintus Bio, Caribou Bio, Ipsen, Miltenyi, Morphosys, Daiichi-Sankyo, ADC Therapeutics, Abbvie, AstraZeneca, Synthekine and research funding from Kite/Gilead and Pfizer.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Neelapu SS, Locke FL, Go WY. CAR T-cell therapy in large B-cell lymphoma. *N Engl J Med*. 2018; 378(11):1065.
2. 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. https://doi.org/10.1056/nejmoa1804980
3. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020; 396(10254): 839-852. https://doi.org/10.1016/s0140-6736(20)31366-0
4. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020; 38(27): 3119-3128. https://doi.org/10.1200/jco.19.02104
5. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *J Clin Oncol*. 2020; 38(27): 3095-3106. https://doi.org/10.1200/jco.19.02103
6. Kuhnl A, Roddie C, Kirkwood AA, et al. A national service for delivering CD19 CAR-T in large B-cell lymphoma - the UK real-world experience. *Br J Haematol*. 2022; 198(3): 492-502. https://doi.org/10.1111/bjh.18209
7. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. *Blood*. 2022; 140(4): 349-358. https://doi.org/10.1182/blood.2021015209

8. Iacoboni G, Villacampa G, Martinez-Cibrian N, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. *Cancer Med*. 2021; 10(10): 3214-3223. https://doi.org/10.1002/cam4.3881
9. Bachy E, Le Gouil S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022; 28(10): 2145-2154. https://doi.org/10.1038/s41591-022-01969-y
10. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022; 386(7): 640-654. https://doi.org/10.1056/nejmoa2116133
11. Abramson JS, Solomon SR, Arnason JE, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of phase 3 TRANSFORM study. *Blood*. 2022; 141(14): 1675-1684. https://doi.org/10.1182/blood.2022018730
12. Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. *J Clin Oncol*. 2022; 40(5): 481-491. https://doi.org/10.1200/jco.21.00931
13. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022; 387(24): 2220-2231. https://doi.org/10.1056/nejmoa2206913
14. Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20xCD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. *Lancet Haematol*. 2022; 9(5): e327-e339. https://doi.org/10.1016/s2352-3026(22)00072-2
15. Dreger P, Fenske TS, Montoto S, Pasquini MC, Sureda A, Hamadani M. Cellular immunotherapy for refractory diffuse large B cell lymphoma in the chimeric antigen receptor-engineered T cell era: still a role for allogeneic transplantation? *Biol Blood Marrow Transpl*. 2020; 26(4): e77-e85. https://doi.org/10.1016/j.bbmt.2019.12.771
16. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med*. 2017; 377(13): 1250-1260. https://doi.org/10.1056/nejmoa1701769
17. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012; 367(6): 520-531. https://doi.org/10.1056/nejmoa1200920
18. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020; 382(14): 1331-1342. https://doi.org/10.1056/nejmoa1914347
19. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. *J Clin Oncol*. 2023; 41(3): 555-567. https://doi.org/10.1200/jco.21.02370
20. Munshi PN, Hamadani M, Kumar A, et al. ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma. *Bone Marrow Transpl*. 2021; 56(12): 2911-2921. https://doi.org/10.1038/s41409-021-01288-9
21. Iacoboni G, Rejeski K, Villacampa G, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2022; 6(12): 3606-3610. https://doi.org/10.1182/bloodadvances.2021006922
22. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022; 23(1): 91-103. https://doi.org/10.1016/s1470-2045(21)00591-x
23. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med*. 2022; 28(2): 325-332. https://doi.org/10.1038/s41591-021-01622-0

24. Salles G, Schuster SJ, Dreyling M, et al. Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. *Blood Adv*. 2022; 6(22): 5835-5843. https://doi.org/10.1182/bloodadvances.2022008150
25. Ghione P, Palomba ML, Ghesquieres H, et al. Treatment patterns and outcomes in relapsed/refractory follicular lymphoma: results from the international SCHOLAR-5 study. *Haematologica*. 2023; 108(3): 822-832. https://doi.org/10.3324/haematol.2022.281421
26. Sureda A, Zhang MJ, Dreger P, et al. Allogeneic hematopoietic stem cell transplantation for relapsed follicular lymphoma: a combined analysis on behalf of the Lymphoma Working Party of the EBMT and the Lymphoma Committee of the CIBMTR. *Cancer*. 2018; 124(8): 1733-1742. https://doi.org/10.1002/cncr.31264
27. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood*. 2020; 136(8): 925-935. https://doi.org/10.1182/blood.2019004000
28. Jain T, Olson TS, Locke FL. How I treat cytopenias after CAR T-cell therapy. *Blood*. 2023. https://doi.org/10.1182/blood.2022017415
29. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. *J Immunother Cancer*. 2022; 10(5):e004475. https://doi.org/10.1136/jitc-2021-004475
30. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood*. 2021; 138(24): 2499-2513. https://doi.org/10.1182/blood.2020010543
31. Miller KC, Johnson PC, Abramson JS, et al. Effect of granulocyte colony-stimulating factor on toxicities after CAR T cell therapy for lymphoma and myeloma. *Blood Cancer J*. 2022; 12(10): 146. https://doi.org/10.1038/s41408-022-00741-2
32. Lievin R, Di Blasi R, Morin F, et al. Effect of early granulocyte-colony-stimulating factor administration in the prevention of febrile neutropenia and impact on toxicity and efficacy of anti-CD19 CAR-T in patients with relapsed/refractory B-cell lymphoma. *Bone Marrow Transpl*. 2022; 57(3): 431-439. https://doi.org/10.1038/s41409-021-01526-0
33. Baur R, Jitschin R, Kharboutli S, et al. Thrombopoietin receptor agonists for acquired thrombocytopenia following anti-CD19 CAR-T-cell therapy: a case report. *J Immunother Cancer*. 2021; 9(7):e002721. https://doi.org/10.1136/jitc-2021-002721
34. Beyar-Katz O, Perry C, On YB, et al. Thrombopoietin receptor agonist for treating bone marrow aplasia following anti-CD19 CAR-T cells-single-center experience. *Ann Hematol*. 2022; 101(8): 1769-1776. https://doi.org/10.1007/s00277-022-04889-6
35. Drillet G, Lhomme F, De Guibert S, Manson G, Houot R. Prolonged thrombocytopenia after CAR T-cell therapy: the role of thrombopoietin receptor agonists. *Blood Adv*. 2023; 7(4): 537-540. https://doi.org/10.1182/bloodadvances.2022008066
36. Rejeski K, Burchert A, Iacoboni G, et al. Safety and feasibility of stem cell boost as a salvage therapy for severe hematotoxicity after CD19 CAR T-cell therapy. *Blood Adv*. 2022; 6(16): 4719-4725. https://doi.org/10.1182/bloodadvances.2022007776
37. Mullanfiroze K, Lazareva A, Chu J, et al. CD34+-selected stem cell boost can safely improve cytopenias following CAR T-cell therapy. *Blood Adv*. 2022; 6(16): 4715-4718. https://doi.org/10.1182/bloodadvances.2022007572
38. Gagelmann N, Wulf GG, Duell J, et al. Hematopoietic stem cell boost for persistent neutropenia after CAR T-cell therapy: a GLA/DRST study. *Blood Adv*. 2023; 7(4): 555-559. https://doi.org/10.1182/bloodadvances.2022008042
39. Stein-Thoeringer CK, Saini NY, Zamir E, et al. A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy. *Nat Med*. 2023; 29(4): 906-916. https://doi.org/10.1038/s41591-023-02234-6
40. Efficace F, Cannella L, Sparano F, et al. Chimeric antigen receptor T-cell therapy in hematologic malignancies and patient-reported outcomes: a scoping review. *Hemasphere*. 2022; 6(12):e802. https://doi.org/10.1097/hs9.0000000000000802

41. Abramson JS, Johnston PB, Kamdar M, et al. Health-related quality of life with lisocabtagene maraleucel vs standard of care in relapsed or refractory LBCL. *Blood Adv*. 2022; 6(23): 5969-5979. https://doi.org/10.1182/bloodadvances.2022008106
42. Elsawy M, Chavez JC, Avivi I, et al. Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. *Blood*. 2022; 140(21): 2248-2260. https://doi.org/10.1182/blood.2022015478
43. Wang XS, Srour SA, Whisenant M, et al. Patient-reported symptom and functioning status during the first 12 Months after chimeric antigen receptor T cell therapy for hematologic malignancies. *Transplant Cell Ther*. 2021; 27(11): 930e931-930e910. https://doi.org/10.1016/j.jtct.2021.07.007
44. Sidana S, Dueck AC, Thanarajasingam G, et al. Longitudinal patient reported outcomes with CAR-T cell therapy versus autologous and allogeneic stem cell transplant. *Transplant Cell Ther*. 2022; 28(8): 473-482. https://doi.org/10.1016/j.jtct.2022.05.004
45. Spanjaart AM, Pennings ERA, Kos M, et al. Development of a core set of patient- and caregiver-reported signs and symptoms to facilitate early recognition of acute chimeric antigen receptor T-cell therapy toxicities. *JCO Oncol Pract*. 2023; 19(3): e407-e416. https://doi.org/10.1200/op.22.00501
46. Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. *Nat Rev Clin Oncol*. 2019; 16(6): 372-385. https://doi.org/10.1038/s41571-019-0184-6
47. Sotillo E, Barrett DM, Black KL, et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. *Cancer Discov*. 2015; 5(12): 1282-1295. https://doi.org/10.1158/2159-8290.cd-15-1020
48. Myers RM, Taraseviciute A, Steinberg SM, et al. Blinatumomab nonresponse and high-disease burden are associated with inferior outcomes after CD19-CAR for B-all. *J Clin Oncol*. 2022; 40(9): 932-944. https://doi.org/10.1200/jco.21.01405
49. O'Brien MM, Ji L, Shah NN, et al. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: children's Oncology group protocol AALL1621. *J Clin Oncol*. 2022; 40(9): 956-967. https://doi.org/10.1200/jco.21.01693
50. Fischer J, Paret C, El Malki K, et al. CD19 isoforms enabling resistance to CART-19 immunotherapy are expressed in B-all patients at initial diagnosis. *J Immunother*. 2017; 40(5): 187-195. https://doi.org/10.1097/cji.0000000000000169
51. Nagel I, Bartels M, Duell J, et al. Hematopoietic stem cell involvement in BCR-ABL1-positive ALL as a potential mechanism of resistance to blinatumomab therapy. *Blood*. 2017; 130(18): 2027-2031. https://doi.org/10.1182/blood-2017-05-782888
52. Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. *Nat Med*. 2021; 27(8): 1419-1431. https://doi.org/10.1038/s41591-021-01436-0
53. Shah NN, Johnson BD, Schneider D, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. *Nat Med*. 2020; 26(10): 1569-1575. https://doi.org/10.1038/s41591-020-1081-3
54. Wang T, Tang Y, Cai J, et al. Coadministration of CD19-and CD22-directed chimeric antigen receptor T-cell therapy in childhood B-cell acute lymphoblastic leukemia: a single-arm, multicenter, phase II trial. *J Clin Oncol*. 2023; 41(9): 1670-1683. https://doi.org/10.1200/jco.22.01214
55. Lee YG, Guruprasad P, Ghilardi G, et al. Modulation of BCL-2 in both T cells and tumor cells to enhance chimeric antigen receptor T-cell immunotherapy against cancer. *Cancer Discov*. 2022; 12(10): 2372-2391. https://doi.org/10.1158/2159-8290.cd-21-1026
56. Jain MD, Zicchеddu B, Coughlin CA, et al. Whole-genome sequencing reveals complex genomic features underlying anti-CD19 CAR T-cell treatment failures in lymphoma. *Blood*. 2022; 140(5): 491-503. https://doi.org/10.1182/blood.2021015008

57. Scholler N, Perbost R, Locke FL, et al. Tumor immune contexture is a determinant of anti-CD19 CAR T-cell efficacy in large B-cell lymphoma. *Nature Med*. 2022; 28(9): 1872-1882. https://doi.org/10.1038/s41591-022-01916-x
58. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. *Blood Adv*. 2020; 4(19): 4898-4911. https://doi.org/10.1182/bloodadvances.2020002394
59. Amini L, Silbert SK, Maude SL, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion. *Nat Rev Clin Oncol*. 2022; 19(5): 342-355. https://doi.org/10.1038/s41571-022-00607-3
60. Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: updated results from a phase I anti-CD22 CAR T-cell trial. *J Clin Oncol*. 2020; 38(17): 1938-1950. https://doi.org/10.1200/jco.19.03279
61. Alizadeh D, Wong RA, Yang X, et al. IL15 enhances CAR-T cell antitumor activity by reducing mTORC1 activity and preserving their stem cell memory phenotype. *Cancer Immunol Res*. 2019; 7(5): 759-772. https://doi.org/10.1158/2326-6066.cir-18-0466
62. Plaks V, Rossi JM, Chou J, et al. CD19 target evasion as a mechanism of relapse in large B-cell lymphoma treated with axicabtagene ciloleucel. *Blood*. 2021; 138(12): 1081-1085. https://doi.org/10.1182/blood.2021010930
63. Moon EK, Wang LC, Dolfi DV, et al. Multifactorial T-cell hypofunction that is reversible can limit the efficacy of chimeric antigen receptor-transduced human T cells in solid tumors. *Clin Cancer Res*. 2014; 20(16): 4262-4273. https://doi.org/10.1158/1078-0432.ccr-13-2627
64. Roddie C, Lekakis LJ, Marzolini MAV, et al. Dual targeting of CD19 and CD22 with bicistronic CAR-T cells in patients with relapsed/refractory large B cell lymphoma. *Blood*. 2023. https://doi.org/10.1182/blood.2022018598
65. Ormhoj M, Scarfo I, Cabral ML, et al. Chimeric antigen receptor T cells targeting CD79b show efficacy in lymphoma with or without cotargeting CD19. *Clin Cancer Res*. 2019; 25(23): 7046-7057. https://doi.org/10.1158/1078-0432.ccr-19-1337
66. Salter AI, Rajan A, Kennedy JJ, et al. Comparative analysis of TCR and CAR signaling informs CAR designs with superior antigen sensitivity and in vivo function. *Sci Signal*. 2021; 14(697). https://doi.org/10.1126/scisignal.abe2606
67. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. *Nat Med*. 2018; 24(1): 20-28. https://doi.org/10.1038/nm.4441
68. Collins MA, Jung IY, Zhao Z, et al. Enhanced costimulatory signaling improves CAR T-cell effector responses in CLL. *Cancer Res Commun*. 2022; 2(9): 1089-1103. https://doi.org/10.1158/2767-9764.crc-22-0200
69. Jung IY, Narayan V, McDonald S, et al. BLIMP1 and NR4A3 transcription factors reciprocally regulate antitumor CAR T cell stemness and exhaustion. *Sci Transl Med*. 2022; 14(670):eabn7336. https://doi.org/10.1126/scitranslmed.abn7336
70. Klebanoff CA, Gattinoni L, Restifo NP. Sorting through subsets: which T-cell populations mediate highly effective adoptive immunotherapy? *J Immunother*. 2012; 35(9): 651-660. https://doi.org/10.1097/cji.0b013e31827806e6
71. Ghassemi S, Durgin JS, Nunez-Cruz S, et al. Rapid manufacturing of non-activated potent CAR T cells. *Nat Biomed Eng*. 2022; 6(2): 118-128. https://doi.org/10.1038/s41551-021-00842-6
72. Cooper ML, DiPersio JF. Chimeric antigen receptor T cells (CAR-T) for the treatment of T-cell malignancies. *Best Pract Res Clin Haematol*. 2019; 32(4):101097. https://doi.org/10.1016/j.beha.2019.101097
73. Maciocia PM, Wawrzyniecka PA, Philip B, et al. Targeting the T cell receptor beta-chain constant region for immunotherapy of T cell malignancies. *Nat Med*. 2017; 23(12): 1416-1423. https://doi.org/10.1038/nm.4444

74. Li Z, An N, Yang K, et al. Donor CD7 chimeric antigen receptor T cell bridging to allogeneic hematopoietic stem cell transplantation for T cell hematologic malignancy. *Transplant Cell Ther*. 2023; 29(3): 167-173. https://doi.org/10.1016/j.jtct.2022.11.013
75. Hu Y, Zhou Y, Zhang M, et al. Genetically modified CD7-targeting allogeneic CAR-T cell therapy with enhanced efficacy for relapsed/refractory CD7-positive hematological malignancies: a phase I clinical study. *Cell Res*. 2022; 32(11): 995-1007. https://doi.org/10.1038/s41422-022-00721-y
76. Yang Y, Lim O, Kim TM, et al. Phase I study of random healthy donor-derived allogeneic natural killer cell therapy in patients with malignant lymphoma or advanced solid tumors. *Cancer Immunol Res*. 2016; 4(3): 215-224. https://doi.org/10.1158/2326-6066.cir-15-0118
77. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020; 382(6): 545-553. https://doi.org/10.1056/nejmoa1910607
78. Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. *Cell Stem Cell*. 2018; 23(2): 181-192e185. https://doi.org/10.1016/j.stem.2018.06.002
79. Li Y, Basar R, Wang G, et al. KIR-based inhibitory CARs overcome CAR-NK cell trogocytosis-mediated fratricide and tumor escape. *Nat Med*. 2022; 28(10): 2133-2144. https://doi.org/10.1038/s41591-022-02003-x
80. Daher M, Basar R, Gokdemir E, et al. Targeting a cytokine checkpoint enhances the fitness of armored cord blood CAR-NK cells. *Blood*. 2021; 137(5): 624-636. https://doi.org/10.1182/blood.2020007748
81. Laskowski TJ, Biederstadt A, Rezvani K. Natural killer cells in antitumour adoptive cell immunotherapy. *Nat Rev Cancer*. 2022; 22(10): 557-575. https://doi.org/10.1038/s41568-022-00491-0