CAR-T cells: New developments and implications in lymphoma

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SUMMARY

Recently, the use of chimeric antigen receptor modified T cells or CAR-T cells has emerged in the therapeutic arsenal of several hematological pathologies, including lymphoma. These CAR-T cells are the product of extensive research on understanding the mechanisms of tumour immunity and are the product of cellular engineering. By combining the specific recognition of an antibody and the activation pathways of a cytotoxic cell, CAR-T cells allow promising clinical results, but they also see the occurrence of side effects that are more specific to these treatments, which it is essential to manage in a multidisciplinary team. Different CAR-T cells are currently available, particularly in diffuse large cell B lymphoma. The trials that have enabled their use differ on many points, including patient selection, the manufacture of the CAR or the pre-therapeutic conditioning. In the future, the use of this expensive therapy could be extended to other lymphomas and new generations of CAR-T cells could emerge.

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INTRODUCTION

Lymphomas are a heterogeneous group of malignant diseases and Non-Hodgkin's lymphomas (NHL) are estimated to be one of the leading cancers in developed countries.[1] Diffuse large B-cell lymphomas (DLBCL) are the most common non-Hodgkin's lymphoma (30-40% of new diagnoses) and represent the prototype of aggressive lymphoma. Although, since the era of immunochemotherapy, in particular R-CHOP regimen (combining rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), the majority of these lymphomas have been cured, approximately 15% of patients are refractory to first-line treatment and 25% of patients relapse after achieving complete remission.[2-4] In relapsed patients, second-line treatment with high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HSCT) may be achieved, but about 50% will ultimately relapse after transplantation.[5] Furthermore, the prognosis for non-responding patients to standard chemotherapy or relapsing after HSCT is very poor.[5] Therefore, therapeutic alternatives are needed to improve the survival of these patients.

In recent years, the use of chimeric antigen receptor (CAR)-T cells, a new class of cellular immunotherapy, is beginning to emerge in the treatment of various malignant diseases including lymphomas.

CAR-T CELLS ANATOMY

Chimeric antigen receptor (CAR) modified T cells, or CAR-T cells, are T cells modified by genetic engineering to target antigens specific to tumour cells. This receptor is a combination, in a single-chain molecule, of the B-cell receptor (BCR) antigen binding site and the T-cell receptor (TCR) activation domain. In contrast to TCR, the chimeric receptor allows specific targeting of the antigen independently of the major histocompatibility complex and thus counteracts certain mechanisms of immune evasion to cancer.[6]

CAR-T cells consist of three main domains: the extracellular domain, which contains heavy and light chain variable domains of a single chain fragment variable monoclonal antibody (scFv) and which directly and specifically recognises the tumour antigen of interest,

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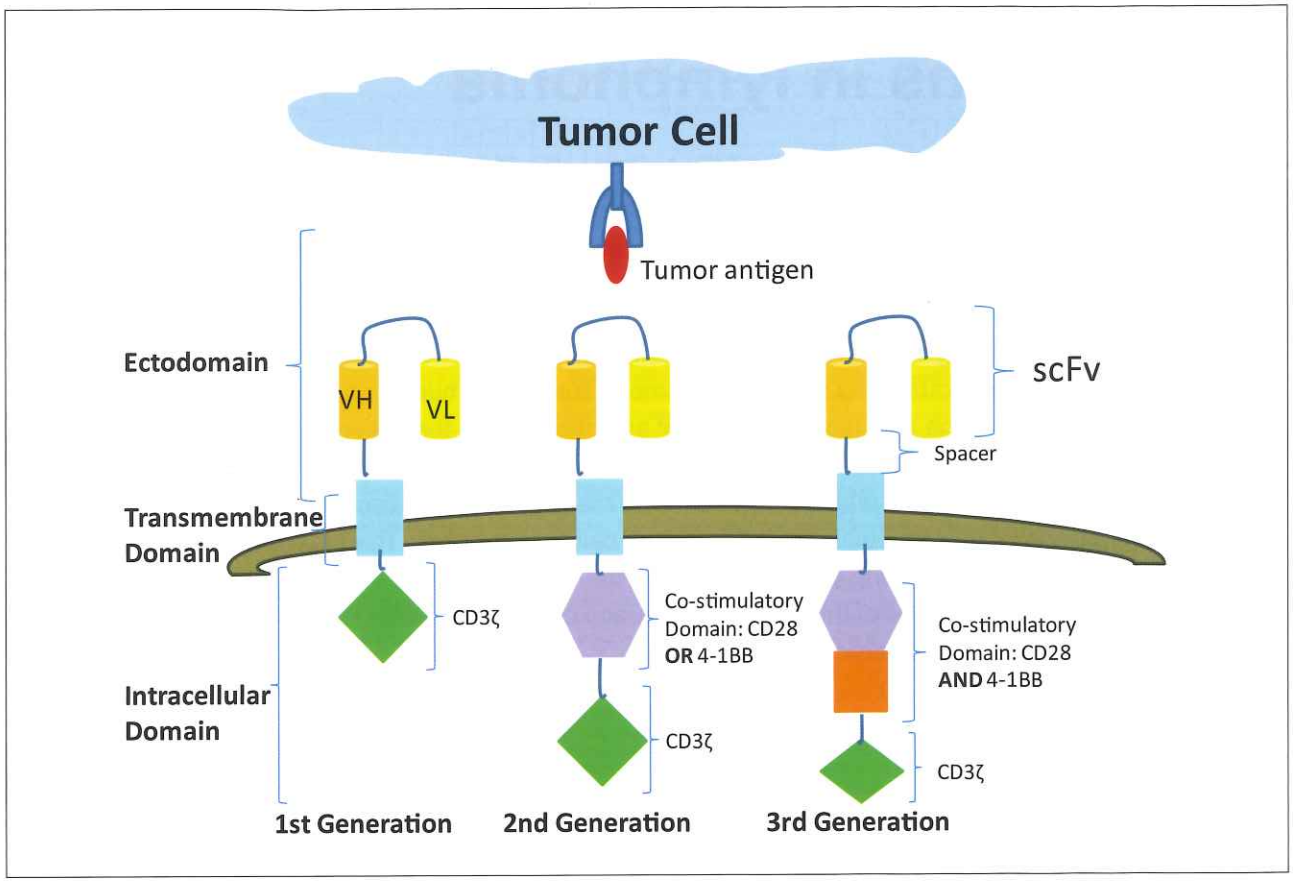

FIGURE 1. CAR-T cells targeting CD19: fundamental concepts and representation of the different generations.
ScFv: single chain fragment variable, VH: heavy chain variable domain, VL: light chain variable domain.

a transmembrane domain and an intracellular domain which allows the activation of T lymphocytes (*Figure 1*).[7]
The first generation of CAR-T cells had, at the level of the intracellular domain, only one CD3ζ chain, which did not allow sufficient cell survival. Subsequently, the development of second generation CAR-T cells, which are those currently available, was marked by the addition, at the intracellular level, of a co-stimulation domain, either CD28 or 4-1BB/CD137, which allows better proliferation and greater long-term persistence. Depending on the choice of co-stimulation domain, it would appear that the proliferation or survival of CAR-T cells would differ. Indeed, CAR-T cells with the 4-1BB co-stimulation domain would persist longer than those with the CD28 co-stimulation domain, but would develop less intensely and less rapidly.[6, 8-10]
A third generation of CAR-T cells is currently undergoing clinical trials,and has as a particularity the association of two intracellular co-stimulation domains including CD28 and 4-1BB (but also OX40, CD27, ICOS, etc.). The objective of this combination is to obtain both a better expansion and a better survival of the CAR-T cells.[11]
In B-cells malignancies, the preferred antigenic target is currently CD19 due to its high expression compared to other targets such as CD20 or CD22. Furthermore, since CD19 expression in normal tissues is restricted to CD19+ B-cells, the main expected on-target, off-tumour effect is a depletion of CD19+ B-cells associated with hypogammaglobulinemia which can be partially compensated for by intravenous immunoglobulin infusion.[12,13]

CAR-T CELLS MANUFACTURING

In eligible patients, the first production step is leukapheresis, which collects peripheral blood mononuclear cells. These cells are then transferred to the manufacturing facilities where T lymphocytes (CD3+ cells) are isolated and then activated, stimulated and transduced with the CAR gene using viral (retroviral or lentiviral) or non-viral vectors. After quality control, the CAR-T cells are usually frozen and shipped to treatment centres. The interval between leukapheresis and injection of CAR-T cells is called the "interval between veins".[8]
In Europe, the interval between veins is estimated at four weeks. Since the diseases are often aggressive with a rapid deterioration of the general condition that can compro-

TABLE 1. Main differences between multicentre studies evaluating second-generation anti-CD19 CAR-T cells in refractory/relapsed aggressive B lymphomas.

Study	ZUMA-1[15]	JULIET[18]	TRANSCEND[20]
CAR-T cell	Axicabtagene ciloleucel (axi-cel, Yescarta®)	Tisagenlecleucel (Kymriah®)	Lisocabtagene maraleucel (liso-cel)
Costimulatory domain	CD28	4-1BB (CD 137)	4-1BB (CD 137)
Vector	Retrovirus	Lentivirus	Lentivirus
Relapse/refractory	relapse	relapse or refractory	relapse or refractory
Subtype of lymphoma	DLBCL, tFL, PMBCL	DLBCL, tFL	DLBCL, tFL (CORE)
Bridging chemotherapy	No	Yes	Yes
Dose	2x10kg 6 (max $2x10^8$)	0,6-6 $x10^8$ (median dose: $3x10^8$)	DL1: $0,5x10^7$ DL2: $1x10^8$
Lymphodepleting chemotherapy	Cy/Flu 500/30 mg/m² (3d)	Cy/Flu 250/25 mg/m² (3d) (73%) Bendamustine 90mg/m²/d(2d) (20%) Nothing (7%)	Cy/Flu 500/30 mg/m² (3d)
≥ 3 lines of therapy	69%	51%	50%
Prior autologous HSCT	21%	49%	38%
Treated/enrolled	101/111	111/165	114/134
Efficacy			
Best ORR (CR)	82% (54%)	52% (40%)	80% (59%)
12-month PFS	44%	66%	NR
12-month OS	59%	49%	63%

DLBCL: diffuse large B cell lymphoma, tFL: transformed follicular lymphoma, PMBCL: primary mediastinal large B-cell lymphoma, HSCT: hematopoietic stem cell transplantation, ORR: overall response rate, CR: complete response, PFS: progression free survival, OS: overall survival.

mise the perfusion of CAR-T cells, bridging chemotherapy is often administered to stabilise the disease. Thereafter, patients receive lymphodepletion chemotherapy, most often based on cyclophosphamide and fludarabine. The aim of this 3-day chemotherapy is not to control the disease but to deplete the regulatory T-lymphocytes in order to receive CAR-T cells. It is followed by a rest period of two to five days before reinjection of the CAR-T cells. This last phase usually requires close hospital monitoring for about two weeks by a multidisciplinary team (haematology, intensive care unit, neurology) in order to manage toxicities, in particular the cytokine release syndrome and neurological toxicities.[14]

CAR-T CELLS IN DIFFUSE LARGE B LYMPHOMAS: RESULTS OF CLINICAL STUDIES

Three reference studies (ZUMA-1, JULIET and TRANSCEND) form the basis for the use of second-generation CAR-T cells in patients with relapsed or refractory aggressive B-cell NHL. In Europe, in 2018, they have led to the marketing authorisation of CAR-T cells in the third-line (or more) treatment of relapsed or refractory (R/R) diffuse large cell B lymphomas (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL). In Belgium, two products are actually available. Yescarta® (axicabtagene-ciloleucel) is indicated for the treatment of adult patients with relapsed/

refractory DLBCL or PMBCL after at least two lines of systemic therapy. Kymriah® (tisagenlecleucel) is indicated for the treatment of b-cell acute lymphoblastic leukaemia refractory or relapsing after transplantation or after the second or more relapses in children and young adults up to 25 years of. Kymriah® is also available for the treatment of adult patients with relapsed or refractory DLBCL after at least two lines of systemic.

There are many differences between these studies, including lymphoma subtype, co-stimulation domain, CAR-T cell dose, conditioning, and whether or not bridging chemotherapy is used. These key characteristics are summarised in *Table 1*.

The results of these studies are often compared with the results of the SCHOLAR-1 retrospective study, which analysed the response rate and survival with rescue chemotherapy in a population of 636 refractory DLBCL patients after one or two lines of treatment or relapsed after HSCT. This study highlighted the poor prognosis of these patients with an overall response rate (ORR), complete response (CR) and median overall survival (OS) of 26%, 7% and 6.3 months respectively.[5]

ZUMA-1[15]

This single-arm phase I and II study, conducted primarily in the U.S., evaluated the safety and efficacy of axicabtagene-ciloleucel (axi-cel) in the treatment of aggressive B-cell NHL. ZUMA-1 included 118 patients with DLBCL, PMBCL or transformed follicular lymphoma (tFL). Eighty-five percent of the patients had stage III or IV disease, 70% were refractory to at least three treatments and 21% had prior autologous-HSCT. Bridging chemotherapy was not allowed but the interval between veins was short with a median duration of 23 days. Of the 111 patients who were included in phase II, 101 (91%) received axi-cel infusion. In treated patients, response was assessed from one month after reinfusion of axi-cel with an ORR and CR at 82% and 54% respectively. It should be noted that in 23 patients with partial response (PR) or stable disease at one month, there was a conversion to CR during follow-up without further treatment. The last update of the data showed that median OS was not achieved at 27.1 months of follow-up while median progression free survival (PFS) was estimated at 5.9 months. At six months, PFS appears to plateau with PFS at 12, 18 and 24 months at 44%, 40% and 39% respectively.[16,17]

JULIET[18]

This pivotal international single-arm phase II study evaluated tisagenlecleucel in adult patients with refractory or relapsed DLBCL or tFL. Tisagenlecleucel (formerly known as CTL019) has previously been approved for the treatment of refractory or relapsed acute B lymphocytic leukaemia in children and young adults. In this study, 51% had already received at least three treatments and 49% were relapsing after autologous HSCT. Unlike the ZUMA-1 study, CAR-T cells could be frozen and bridging chemotherapy was administered in 90% of patients, which is more in line with clinical practice. The median duration of the interval between veins was 54 days. Of the 165 patients included in the study, only 111 patients (67%) benefited from CAR-T cell reinfusion. The main causes of non-reinfusion were disease progression or death in 38 patients and a production problem in twelve patients. In addition, four patients had not yet been infused by the data cut-off date. In the 99 evaluable patients (≥3 months of follow-up), the best ORR and CR were 54% and 40% respectively. At nineteen months of follow-up, median OS was approximately eleven months but median survival was not achieved in CR patients. Similar to ZUMA-1, a significant number of PR patients converted their response to CR during follow-up.[16,18,19]

TRANSCEND[2]

This multicentre phase I study evaluates lisocabagen maraleucel (liso-cel) which has a defined composition of CD4+ and CD8+ cells. Inclusion criteria were broader than ZUMA-1 and JULIET: R/R DLBCL, tFL, follicular lymphoma (FL) grade 3B, mantle cell lymphoma (MCL) and PMBCL. Bridging chemotherapy was permitted and unlike the two previous trials, allograft patients and those with central nervous system involvement could be included. This study has the particularity of being divided into two cohorts: the first, the "FULL" cohort which evaluates dose escalation and the second, the pivotal "CORE" cohort which included only DLBCL, NOS (de novo or tFL) and high grade B-cell lymphoma (double/triple hit). A recent up-date presented at ASH 2019 showed that out of 342 patients who received leukapheresis, 268 received liso-cel reinfusion. Of the 256 patients whose efficacy was evaluable, the ORR and CR was 73% and 53% respectively. The median duration of response was not reached after a median follow-up of twelve months. The median PFS was approximately seven months and OS was 21.1 months.[16,21,22]

TOXICITY AND SIDE EFFECTS

The two main toxicities of CAR-T cells are cytokine release syndrome (CRS) and neurological toxicity. CRS is a systemic inflammatory reaction that follows the release of pro-inflammatory cytokines (interleukin (IL)-1, IL, 2, IL-6,

TABLE 2. Main ongoing studies in indolent lymphoma.

Study	CAR-T cell	Subtype of lymphoma	Evaluated treatment line	Bridging
ZUMA-2	KTE-X19	MCL	3rd line (prior auto-HSCT allowed)	Yes
ZUMA-5	Axi-cel	FL, MZL	3rd line (prior auto-HSCT allowed)	Yes
ELARA	Tisagenlecleucel	FL	3rd line (prior auto-HSCT allowed)	Yes

MCL: mantle cell lymphoma, FL: follicular lymphoma, MZL: marginal zone lymphoma, HSCT: hematopoietic stem cell transplantation.

etc.) in the course of CAR-T cell activation. It usually appears between a few hours and fourteen days after reinfusion of CAR-T cells and can in rare cases lead to death. The treatment of severe forms, in addition to symptomatic management, is based on the administration of a monoclonal antibody targeting the IL-6 receptor, tocilizumab, with or without corticosteroids. Although long controversial, the use of corticosteroids does not appear to decrease the response to CAR-T cells.[23,24] The neurological toxicity of CAR-T cells or CAR-T cell-related encephalopathy syndrome (CRES) gives rise to a wide variety of manifestations ranging from slight cognitive defects to severe forms of seizures and even death. CRES may or may not occur simultaneously with CRS. Although CRES is secondary to cytokine activation, its mechanism remains imperfectly understood, and tocilizumab does not appear to provide any benefit and corticosteroids remain the recommended therapy.[23-25] Of the three trials cited above, three treatment-related deaths were reported (two in the ZUMA-1 study and one in the TRANSCEND study). Although it is difficult to compare the frequency and severity of toxicities between the studies due to the many differences in the population, conditioning chemotherapy and the grading system of RSCs (use of Lee criteria in ZUMA-1 and TRANSCEND and use of UPenn criteria in JULIET), the toxicity appears to be relatively similar with 12-28% grade 3-4 neurological toxicity and 2-22% grade 3-4 CRS.[15,16,18,24]

Finally, although less well known about CRS, CRES and hypogammaglobulinemia, another frequent toxicity is the appearance of early or late cytopenias (after 30 days). In the later situation, it can occur in up to 30% of cases. The underlying pathophysiological mechanisms are complex and not yet fully elucidated.[26]

REAL-LIFE EXPERIENCE

The first real-life studies seem to confirm the interesting results of these three clinical studies. In an American multicentre retrospective study, evaluating axi-cel in relapsed/refractory large B-cell lymphoma, out of the 298 patients included, 275 (92%) benefited from reinfusion. It should be noted that 43% of the patients would not have been included in ZUMA-1 and that bridging chemotherapy was administered in 53% of cases. Among the 275 patients who benefited from axi-cel reinjection, the best ORR and CR rates were 82% and 64%, respectively. The safety profile and use of tocilizumab corticosteroids were similar to ZUMA-1.[27] Another retrospective study evaluated axi-cel in 108 patients with aggressive NHL B, 52% had received bridging chemotherapy and 60% did not meet the inclusion criteria for ZUMA-1. Of the 95 patients evaluable for response, the best ORR and CR was 71% and 44%, respectively.[28] In Europe, a retrospective study of LYSA conducted in five French centres included 60 relapsed or refractory DLCBLs (median of three treatment lines) treated with axi-cel or tisagenlecleucel. Despite a low median follow-up (about five months), the results were encouraging with an estimated 54% PFS at three months and 82% OS. It should be emphasised that the majority of patients received bridging chemotherapy.[29]

CAR-T CELLS IN OTHER LYMPHOMAS

There is much less data in the literature regarding the use of CD19 CAR-T cells in the treatment of other lymphomas such as FL and MCL.

Patients with R/R MCL despite treatment with a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib or acalabrutinib) have a poor prognosis. Recently, results were published on the efficacy and safety of ZUMA-2 which is a multi-center phase II study evaluating KTE-X19 in the treatment of relapsed or refractory mantle cell lymphomas after treatment with a BTK inhibitor. KTE-X19 is similar to axi-cel but its manufacturing process removes circulating CD-19 expressing malignant cells, thereby reducing the activation and eventual depletion of anti-CD19 CAR-T cells during

the ex-vivo manufacturing process. Of the 74 patients included in the study, KTE-X19 was administered to 68 (92%) after conditioning chemotherapy with fludarabine and cyclophosphamide. The median age was 65 years, 81% had at least three lines of prior therapy, 43% had relapsed after autologous HSCT, and 62% were refractory to the BTK inhibitors. Of the 60 patients with at least seven months follow-up, 93% had an objective response and 67% had a CR (after a median of three months). At twelve months, the estimated PFS and OS were 61% and 83%, respectively. It should be noted that many patients with stable disease or PR subsequently had a CR. In addition, it would appear that the response was similar in patients with markers of poor prognosis (pleomorphic variants, TP53 and Ki-67 mutation >50%). Of the 68 patients who benefited from KTE-X19 administration, 99% had a grade 3 or higher side effect with in particular 94% cytopenias (sometimes prolonged) of which 84% were neutropenias and 32% infections. Although they were not responsible for death, CRS and neurological toxicity of grade 3 or higher were found in 15% and 31%, respectively. Of the sixteen patients who died, two died because of side effects.[30]

Nevertheless, following some encouraging results in small series, several clinical studies evaluating CAR-T cells in the treatment of R/R FL and marginal zone lymphoma (MZL) are ongoing (*Table 2*).[31,32] An interim analysis of the phase II ZUMA-5 study (NCT03105336), evaluating axi-cel in patients with R/R indolent NHL, was presented at the American Society of Clinical Oncology 2020 meeting. Of the 94 patients who received axi-cel (80 LF; 14 MZL), 73% were refractory to the last prior treatment with a median of three prior treatments. Of the 87 patients (80 LF and 7 MZL) who achieved an evaluable response, the ORR was 94% with 79% ORR.[33]

Hodgkin's lymphoma (HL) in its classic form expresses CD30 almost ubiquitously, which is already a therapeutic target used in R/R diseases. CAR-T cells targeting CD30 are being developed in R/R HL, with modest preliminary results but an acceptable safety profile.[34]

FUTURE OF CAR-T CELLS IN LYMPHOMA

Although CAR-T cells have good results in the treatment of R/R DLBCL, 50-60% of patients do not obtain CR or relapse after CAR-T cell treatment. Understanding resistance mechanisms is essential in order to find ways to improve the efficacy of existing CAR-T cells or to ensure the development of new CAR-T cells.

Loss of tumour expression of the extracellular CD19 epitope that binds to the CAR is a well-described resistance mechanism in acute lymphoblastic leukemia.[35] Although less well described, this mechanism may be involved in relapse after CAR T cell therapy in DLBCL.[36,37] In addition, in the ZUMA-1 study, the authors describe a loss of CD19 expression on tumour biopsies in three of eleven patients (27%) who relapsed after CAR T cell therapy.[15] To counteract this loss, new so-called bispecific CAR-T cells that simultaneously target two distinct antigens are being developed. In lymphoma, the first CAR-T cells under development target CD19 with CD20 or CD22. Preliminary studies seem to show interesting results with an acceptable safety profile.[38,39]

Another suspected resistance mechanism is increased activation of the programmed cell-death 1/programmed cell-death 1 ligand (PD1/PDL-1) pathway.[40,41] Although early retrospective data suggest that the combination of CAR-T cells and PD1 inhibitors in B-NHL is feasible and safe, several phase I and II studies evaluating this combination are ongoing.[40,42]

At present, there are many other pathways being investigated in the CAR-T cell pipeline. The first would be the development of fourth generation CAR-T cells or T cells redirected for universal cytokine killing (TRUCK) which have a specific synthesis capacity of one or the other protein (IL-1, IL-2, IL-6, etc.), which would renounce the activation of the CAR-T cell.[43] A second option would be the use of allogeneic CAR-T cells, collected from healthy volunteers, which would have the advantage of having CAR-T cells directly ready for use. However, there are still some obstacles to their use, such as a possible graft-versus-host reaction following recognition by the HLA system by the TCR or a rejection of these cells by the recipient's immune system because they express histocompatibility antigens distinct from those of the patient. Finally, the future of CAR-T cells may lie in the use of natural killer cells with a CAR (CAR-NK cells). Indeed, a phase I and II study recently evaluated the interest of allogeneic CAR-NK cells targeting CD19 in patients with relapsed or refractory B-cell NHL or chronic lymphocytic leukaemia. Of the eleven patients included, eight had a response (including seven CR) with an absence of CRS, neurological toxicity or graft-versus-host disease.[44]

Patients with secondary central nervous system (CNS) lymphomas were excluded from the pivotal studies due to fear of excessive brain toxicity. Nevertheless, Frigault *et al.* report in a retrospective study of eight patients that the use of tisagenlecleucel has a safety profile in patients with aggressive B-cell NHL with secondary CNS involvement similar to that observed in patients without active CNS disease. In addition, four of the eight patients had at least a partial response. Although further studies are needed

KEY MESSAGES FOR CLINICAL PRACTICE

1. **The position of anti-CD19 CAR-T cells in the therapeutic algorithm for R/R DLBCL is becoming clearer by the day.**
2. **In clinical practice, bridging chemotherapy is often necessary because the interval between leukapheresis and infusion of CAR-T cells can take several weeks.**
3. **CAR-T cells may be responsible for toxicities such as cytokine release syndrome and CAR-T cell-related encephalopathy syndrome that require management by a multidisciplinary team.**
4. **The high cost of CAR-T cells requires careful selection of the patients who will benefit the most from this treatment.**

to confirm these results, this study opens the way for the use of CAR T-cells in secondary CNS lymphoma and even primary CNS lymphoma.[45]

CONCLUSION

The position of anti-CD19 CAR-T cells in the therapeutic algorithm for relapsed or refractory DLBCL is becoming clearer by the day. Although the results are promising, about 50% of patients still die from their lymphoma and we have little experience with their long-term efficacy and side effects. In addition, the use of CAR-T cells represents a significant cost (exceeding 400,000 euros) and remains a challenge in current clinical practice. It is therefore essential to identify the factors that will allow us to best target the patients who could benefit from this treatment. Finally, the future of these treatments requires new developments in order to improve their efficacy, better understand the mechanisms of resistance, reduce their toxicity and extend their field of activity.

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