Integration of cell therapies and bispecific antibodies into the treatment pathway of relapsed diffuse large B-cell lymphoma

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL) representing 30–40% of all cases.[1] It is a heterogeneous B-lymphoid neoplasm that consists of subtypes distinguished by clinical, cytogenetic, and molecular features, with variable outcomes when treated with upfront immunochemotherapy. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) is the current standard for first-line immunochemotherapy for DLBCL, with 60–70% of patients being cured by this approach. However, 10–15% of patients have primary refractory disease and a further 20–30% relapse after first-line treatment.[2] The International Prognostic Index (IPI) and age-adjusted IPI are risk stratification tools used since 1993 to identify individuals that will respond poorly to doxorubicin-containing chemotherapy regimens based on clinical variables; age, performance status, tumour stage, number of extranodal sites, and serum LDH level.[3] This prognostic scoring system remains valid in the rituximab era. Biological features of the disease also have prognostic relevance including the cell-of-origin (germinal centre B-cell and activated B-cell, as identified by gene expression profiling),[4–6] genetic rearrangements in c-MYC in addition to BCL2 and/or BCL6 (double/triple-hit lymphoma)[7–10] and expression of c-myc and Bcl2 in the absence of underlying genetic changes (double expressor lymphoma; Green *et al*, JCO 2012; Johnson *et al*, JCO 2012; Horn *et al*, Blood 2013).

The current standard of care for relapsed/refractory disease for eligible patients remains non cross-reacting relapse therapy with platinum-based or ifosfamide-containing regimens, incorporating an anti-CD20 monoclonal antibody[2,11] followed by autologous stem-cell transplantation (ASCT).[2,11] Results of the prospective CORAL study, evaluating the efficacy of R-ICE compared to R-DHAP as salvage regimens, demonstrated that only 50% of relapsed/refractory patients were able to undergo ASCT largely due to failure to adequately respond to second line therapy. This was more common among patients with higher secondary age-adjusted IPI score, prior rituximab treatment, and refractory disease/relapse less than 12 months after diagnosis.[11] Other reasons for ineligibility for aggressive approaches include advanced age, comorbidities, and less commonly, failure to collect stem cells. Failure of response to first-line salvage treatment or relapse post ASCT results in extremely poor outcomes.[12] For those patients who could not proceed to ASCT in the CORAL study, median overall survival was 4.4 months from failing response.[13] The curability of these patients with second-line relapse regimens is limited; nevertheless, a minority of relapsed/refractory patients will respond to third-line regimens and may be considered for allogeneic stem cell transplant.[13,14]

For transplant-ineligible patients with relapsed/refractory disease median overall survival remains very poor at less than 4 months.[15] Treatment options include conventional chemotherapy with or without rituximab, localized radiotherapy, supportive care, or enrolment in clinical trials. Table 1 demonstrates response rates in the trial setting for recently approved therapies in relapsed/refractory and transplant-ineligible patients. These include antibody-drug conjugates: Polatuzumab vedotin and loncastuximab tesirine, tafasitamab (CD19-targeting monoclonal antibody), and selinexor (oral nuclear export inhibitor). Polatuzumab vedotin (targeting CD79b, a B-cell receptor

Table 1. Response rates in the trial setting for recently approved therapies in relapsed/refractory and transplant-ineligible patients.

Drug combination	Comparator	OR (%)	CR (%)	PFS (median, months)	OS (median, months)
Polatuzumab Vedotin + Bendamustine + Rituximab[16] $n = 40$	Bendamustine + Rituximab $n = 40$	45	40 *versus* 17.5	9.5 *versus* 3.7	12.4 *versus* 4.7, (median follow-up 22.3 months)
Tafasitamab + lenalidomide $n = 80$[17]		60	43	12.1	Median not reached at 19.6 months follow up, 64% survival at 18 months
Selinexor[18] $n = 127$		28	15	3.5	9.1
Loncastuximab tesirine[19] $n = 145$		48.3	24.1	4.9	9.9

CR, complete response; OR, objective response (defined as the proportion of patients who achieved either complete response or partial response); OS, overall survival; PFS, progression free survival.

component) combined with Bendamustine and rituximab (BR) has been licenced in some countries based on superior progression free and overall survival results in a randomized phase II trial compared with BR alone,[16] while the results of the POLARIX trial where it is used in the first-line setting alongside R-CHOP are eagerly awaited. The FDA granted accelerated approval of tafasitamab plus lenalidomide, selinexor and more recently loncastuximab tesirine for adult patients with relapsed/refractory DLBCL based on high and durable overall response rates.[17–19] Enrolment in clinical trials of novel approaches, including cellular therapies and bispecific antibodies, are becoming increasingly important in targeting this unmet need.

Advent of CAR-T cells

The recent development in genetic engineering of T-cells to express chimeric antigen receptors (CAR-T cells) has led to the availability of an effective new option for patients with relapsed/refractory (R/R) DLBCL associated with high responses rates and durable responses for some patients. CARs are fusion proteins that combine a monoclonal antibody-derived single chain variable fragment recognizing cancer-specific epitopes with a T-cell activation domain derived from the intracellular portion of the T-cell receptor. Second- and third-generation CARs also incorporate co-stimulatory domains such as CD28 and/or 4-1BB.[20] Initial preclinical studies demonstrating the potential for use of CARs in eliminating B-cell malignancies expressing CD19, a ubiquitous B-cell marker, were published in 2003.[21] Since then, multiple single and multicentre trials of anti-CD19 CAR-T cells have demonstrated therapeutic efficacy in R/R B-cell malignancies with a significant number of patients achieving complete and sustained remissions (Table 2).[22,23] Axicabtagene ciloleucel (axi-cel) and Tisagenlecleucel are two CAR-T cell products currently licenced for the treatment of R/R DLBCL based on the results of pivotal multicentre trials. The Zuma-1 phase II multicentre study investigating axi-cel therapy, a CD-19 specific CAR containing a CD28 co-stimulatory domain, in patients with R/R large B-cell lymphomas demonstrated a complete response (CR) rate of 58% with a median overall survival of greater than 2 years.[24,25] Findings from the international phase II JULIET study of tisagenlecleucel, an anti-CD19 CAR containing a 4-1BB co-stimulatory domain, in patients with R/R DLBCL who were ineligible for or had disease progression after autologous stem-cell transplantation demonstrated a CR rate of 40%, sustained in 79% of these patients at 12 months.[26] A third product, lisocabtagene maraleucel—an anti-CD19 4-1BB CAR, has recently been approved by the FDA following the results in the phase II TRANSCEND

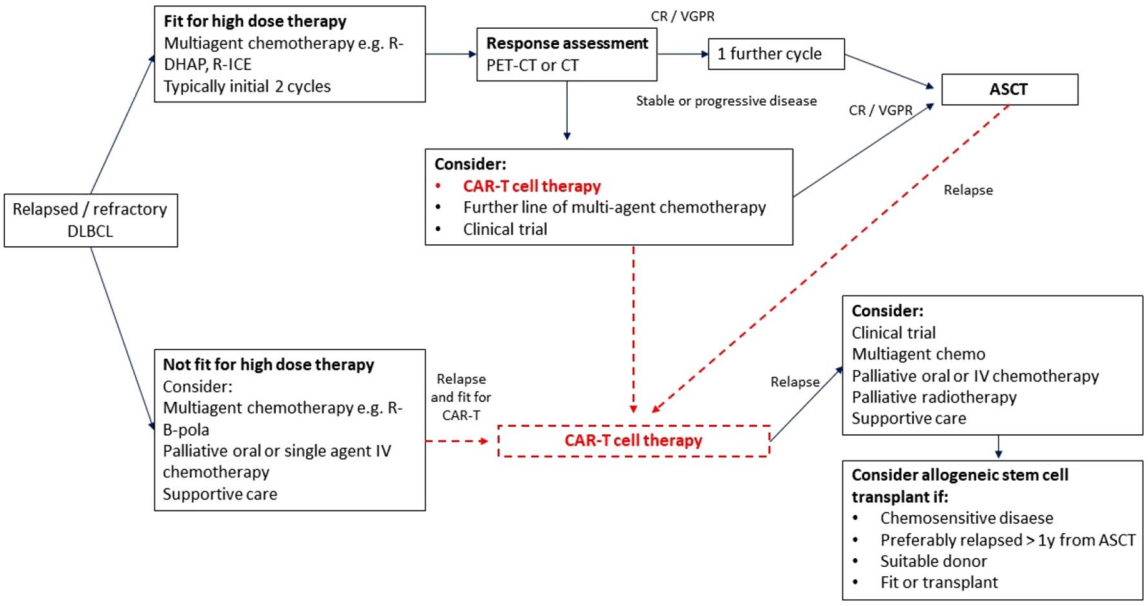

Figure 1. Pathway for relapsed/refractory DLBCL.
ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptors-T cells; CR, complete response; CT, cell transplantation; DLBCL, diffuse large B-cell lymphoma; PET, positron emmission tomography; R-B-pola, rituximab, Bendamustine, polatuzumab vedotin; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; VGPR, very good partial response.

study demonstrating high durable CR rates in heavily pretreated R/R DLBCL patients.[27,28] A recent meta-analysis evaluating 11 trials of second-generation CAR products in B-cell NHLs reported objective response rates and CR rates of 68% and 46% in 306 patients with R/R DLBCL, mostly anti-CD19 CARs. When compared with results of the recent retrospective SCHOLAR-1 study evaluating outcomes in refractory DLBCL, objective response rate and CR rates to next line of salvage therapy were 26% and 7%, respectively, with a median overall survival of 6.3 months.[29] CAR T-cell therapies therefore hold promise for this cohort of patients. Indeed, since the approval of these treatment the pathway for patients with R/R DLBCL has changed dramatically (Figure 1).

In addition to CD19, other antigens have been the target of CAR T-cell development for the treatment of lymphoma including CD20, kappa light chain antigen and CD22 in B-cell NHLs.[20] Interpretation of the efficacy of CAR-T products, however, is limited by heterogeneity in trial methodology, CAR-T design and patient selection—including NHL subtype-specific disease variables, prior ASCT, differences in prior lines of therapy and the use of conditioning therapy. The utility in clinical practice of these products is limited by their cost, time to access and eligibility (especially for patients with quickly progressive disease and comorbidities) and toxicity including cytokine release syndrome (CRS) and neurotoxicity reported at rates of as high as 40%.[30] In order to improve CAR-T-cell therapies, reducing the risk of such toxicities is imperative. Furthermore, the majority of patients treated with licenced products relapse with identified possible mechanisms being CD19 negative escape[24] and CAR-T exhaustion. An ongoing trial of a new CD19 CAR-T product aims to mitigate that by using a 'fast-off' approach which has a more physiological contact time between the CAR and the target. This approach could reduce toxicity and increase persistence {Claire Roddie, 2020 #1727}

Bispecific antibodies

Bispecific antibodies (BSA) employ a similar mechanism of action to CAR T-cells in that they redirect T-cell effector functions towards cells expressing target cancer-specific epitopes. A forerunner of BSAs was Blinatumomab which was approved by the FDA in 2014 for the treatment

Table 2. Summary of results of approved CAR-T cell products in phase II trials for relapsed/refractory DLBCL.

Clinical trial *n* = enrolled (infused)	CAR-T product	OR (%)	CR (%)	PFS (median, months)	OS (median, months)	Median turnaround time for manufacturing to delivery/ infusion (days)	Relevant toxicity (grade 3 or higher)
ZUMA-1[24] *n* = 111 (101)	Axicabtagene ciloleucel (Apheresis to infusion efficacy: 99%)	82	58	5.8 6 months: 49% 12 months: 44%	Median not reached. 6 months: 78% 12 months: 59%	17	95% Neutropenia 78% Neurotoxicity 28% CRS 13%
JULIET[26] *n* = 165 (111)	Tisagenleucel	52	40	Not reached. Estimated 12 months: 83%	12 12 months: 49%	54	89% Cytopaenias 16% CRS 22% Neurotoxicity 12%
TRANSCEND-001[28] *n* = 344 (269)	Lisocabtagene maraleucel (Apheresis to infusion efficacy: 78%)	73	53	6.8 6 months: 51.4% 12 months: 44%	21.1 6 months: 74.7% 12 months: 58%	37	79% Neutropenia 60% Neurotoxicity 10% CRS 2%

CAR-T, chimeric antigen receptors-T cells; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; OR, objective response (defined as the proportion of patients who achieved either complete response or partial response); OS, overall survival; PFS, progression free survival.

of B-acute lymphoblastic leukaemia. It is a bispecific T-cell engager (BiTE) with two single-chain variable fragments containing antigen binding sites that recognize both CD19 and CD3 T cell receptor complex, resulting in T-cell activation and effector function.[31] However, these molecules lack the Fc region of the antibody. Their small size means that they are filtered by the kidneys which necessitates a continuous infusion as the preferred mode of delivery. This creates many logistical and practical challenges that limits their widespread use. In addition, they lack the potential benefits of a broader activation of the immune system driven by the presence of the Fc receptor. BSAs retain the Fc region of the antibody, while having two different chain variable fragments allowing them to target two different antigens (Figure 2). The retention of the Fc region makes the molecule more stable, having a half-life of 10 days, while it can also be employed to induce a non-T-cell antitumour response by activating complement and other Fc-mediated immune effector cells. They also appear to have a much lower incidence of CRS and neurotoxicity and have demonstrated an overall good safety profile in early phase trials.

Epcoritamab is a BSA against CD20 and CD3 which utilizes the DuoBody® technology. DuoBody® technology is used as a platform to speed up academic and commercial manufacturing of bispecific antibodies.[38] It involves the manufacturing of two separate monoclonal antibodies which are combined to form the final product. Epcoritamab has shown promising preclinical efficacy with high rates of *in vitro* cytotoxicity activity against malignant B-cells from patients with non-Hodgkin lymphomas including DLBCL.[39] In a phase I/II trial, it was shown to have an overall response rate (ORR) of 66.7%. Most importantly, patients who already had CAR-T therapy have responded to this BSA with no reported grade 3 or above toxicity. Further evaluation of this agent is underway.[40]

Glofitamab is BSA targeting CD20 and CD3, but instead of using a 1:1 format, it facilitates bivalent binding to CD20 and monovalent binding to CD3 in a 2:1 format. Recent data from a phase I trial evaluating glofitamab in R/R B-cell non-Hodgkin lymphoma demonstrated an overall response rate of 65.7%, with a complete response in 57.1% of patients dosed at the recommended phase II dose. 84.1% of patients maintained CR with a maximum of 27.4 months. The most common adverse event was CRS occurring in >50% of patients, but this was manageable with only 3.5% of patients experiencing grade 3 or 4 CRS. Despite this

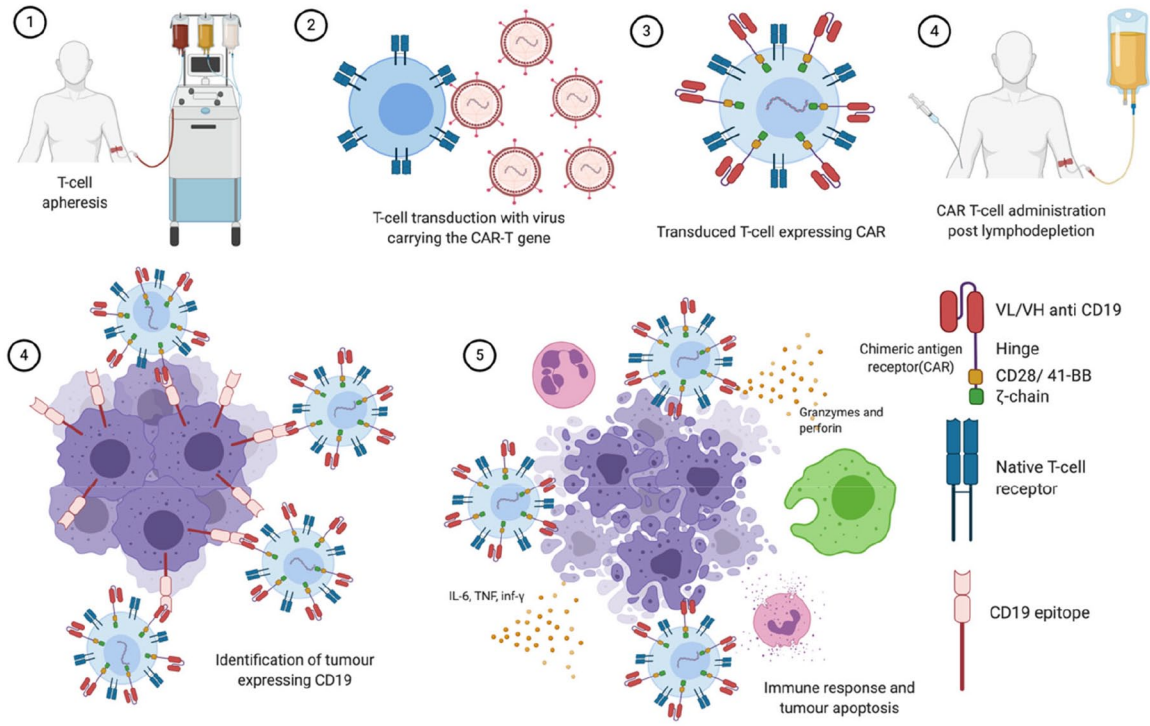

Figure 2. Step 1: Collecting CD3+ T-cell apheresis from the patient is the first step towards making the CAR T product. A minimum of 0.6 × 10*9 and an ideal of 2 × 10*9 cells is usually required.[32] Although the number of cells required is not very high, these patients are often pretreated with steroid, monoclonal antibodies and cytotoxic medication that renders them lymphopenic and this can make harvesting adequate numbers of cells challenging. Despite this, in a cohort of 71 patients, the minimum cell dose was achieved in 97% and the ideal target in 77% of the patients.[32] Step 2: The collected product is washed and the collected T-cells are activated and expanded by various techniques, a process that enables them to obtain a memory phenotype and become less resistance to transduction[33] A lentivirus or retrovirus vector is used to insert the genetic material into the T-cells. Step 3: The genetic material is incorporated into the T-cells' DNA transforming them into a chimeric receptor T-cells.[34] This genetic material expresses a single chain fragment anti CD19 which is connected to a co-stimulatory transmembrane molecule (either CD28 or 4-1BB) and a CD3-ζ chain which is the cytoplasmic signalling domain that will activate the T-cell.[35] Step 4: The cells are re-infused to the patient. Step 5: Within a few days the CAR-T identify their target, become activated and expand. This can be monitored by flow cytometry as CAR-Ts carry a specific signature, while other markers on their surface determine their status (fatigue, activity, etc). The time of activation, the level of expansion and the persistence in the blood may be determined by the co-stimulatory molecule of each product.[36] Step 5: The CAR-T cells induce a strong immunological response. This immunological response is driven by a cytokine release of TNFa, Interleukin-6, interferon-γ, while it also attracts other cells, mainly macrophages which contribute to the immune response.[37] The tenacity of this phenomenon can determine the severity of cytokine release syndrome which is one of the main CAR-T-related toxicities.
CAR-T, chimeric antigen receptors-T cells; DNA, deoxyribonucleic acid; VH, variable heavy chain; VL variable light chain.

glofitamab had good tolerability (only five patients withdrew because of adverse events).[41]

Mosunutuzumab (M) is a fully humanized IgG1 BSA targeting CD20 and CD3. A phase I/IB study evaluated the efficacy and safety of Mosunetuzumab in R/R NHL patients as a single agent.[42] In aggressive NHL, 22/119 (18.6%) achieved a CR with 15/22 (68.2%) of those achieving a durable remission. In addition, expansion of previously administered CAR-Ts after administration of Mosunetuzumab was detected indicating that the ability to bind to CD3 may not only activate native T-cells, but also CAR-T cells that retain their TCR. Preliminary data from the ongoing GO40515 (NCT03677141) study evaluating

Table 3. Summary of response rates and relevant toxicities of bispecific antibody products in clinical trials as single agents for B-cell non-Hodgkin lymphomas.

Bispecific antibody	OR (%)	CR (%)	PFS (median, months)	OS (median, months)	Relevant toxicity (grade 3 or higher)
Epcoritamab[40] $n = 67$	66.7	33.3	NA	NA	No grade 3 or higher CRS Transient neurotoxicity 3%
Glofitamab[41] $n = 171$	53.8	36.8	2.9 in aggressive NHL	NA	56.7% Neutropenia 25.1% CRS 3.5%
Mosunutuzumab[42] $n = 119$	34.7	18.6	NA	NA	Neurotoxicity 3.2% CRS 1.4%
Odronextamab[44] $n = 127$	60% (No prior CAR-T) 33.3% (Prior CAR-T)	60% (No prior CAR-T) 23.8% (Prior CAR-T)	11.1(No prior CAR-T) 2.5 (Prior CAR-T)	NA	Neurotoxocity 3.9% CRS 7.1%

CAR-T, chimeric antigen receptors-T cells; CR, complete response; CRS, cytokine release syndrome; NA, not available; NHL, non-Hodgkin lymphoma; OR, objective response (defined as the proportion of patients who achieved either complete response or partial response); OS, overall survival; PFS, progression free survival.

combination of M-CHOP in R/R and newly diagnosed patients with DLBCL confirms high response rates and a promising tolerability profile.[43] ORR and CR rates in patients with R/R NHL were 86% and 71% and in newly diagnosed patients were 96% and 85%, respectively. No patients had grade $\geqslant 3$ CRS or neurotoxicity. Other combinations, such as M with polatuzumab vedotin, are now currently being investigated.

Odronextamab is another CD20/CD3 BSA using a fully humanized IgG4 platform. A phase I study (NCT02290951) and updated safety and efficacy data from this study demonstrate durable CRs that extend to patients refractory to CAR-T therapy (Table 3). In 127 heavily pre-treated patients with R/R Non-Hodgkin lymphoma, Grades 3 and 4 CRS were reported in only nine patients and resolved with supportive measures. In the higher dose groups, CR rates of 60% were observed in patients with R/R DLBCL with median response duration of 10.3 months.[44]

Overall, there are many promising BSAs which have demonstrated an excellent safety profile with promising response rates in early-phase clinical trials. Interestingly, their ability to bind to CD3+ T-cells means that they could have a synergistic effect with CAR-T cells that retain their native TCR. It is reasonable to expect that some of these results will be replicated in larger phase III trials which could lead to their regulatory approval.

BSAs *versus* CAR-T cells

Figure 4 summarises the benefits and limitiation sof CAR-T and BSAs. In a retrospective evaluation, the relapse rate after axi-cel or tisagenlecleucel for R/R DLBCL patients was 55% at a median follow-up of 9 months.[45] Mechanisms postulated for progression through CAR T-cell therapy include resistance mediated by loss of target antigen, in this case CD19, and lack of CAR-T persistence due to exhaustion or poor expansion. The development of bispecific antibodies targeting CD20 antigen (pan B-cell surface protein) may offer an additional line of treatment in the event of CAR T-cell resistance/relapse or even as adjunctive treatment. Clinical trials of anti-CD20/CD3 bispecific antibody products are ongoing with promising results as mentioned above. These drugs hold promise for R/R disease, including in the setting of relapse after CAR-T therapy as preliminary results suggest that bispecific antibodies may help overcome therapeutic resistance/exhaustion of CAR-T cells and augment their antitumour activity. The incidence of adverse events leading to treatment withdrawal in these studies was low and the incidence of cytokine release syndrome was mostly of grade 1–2 severity. In addition to promising efficacy and favourable tolerability, bispecific antibodies do not require individualized manufacturing, allowing for quicker access for patients with limited prognosis or faster relapsing disease that is difficult to control in the time required to manufacture autologous CAR-T cells. Currently,

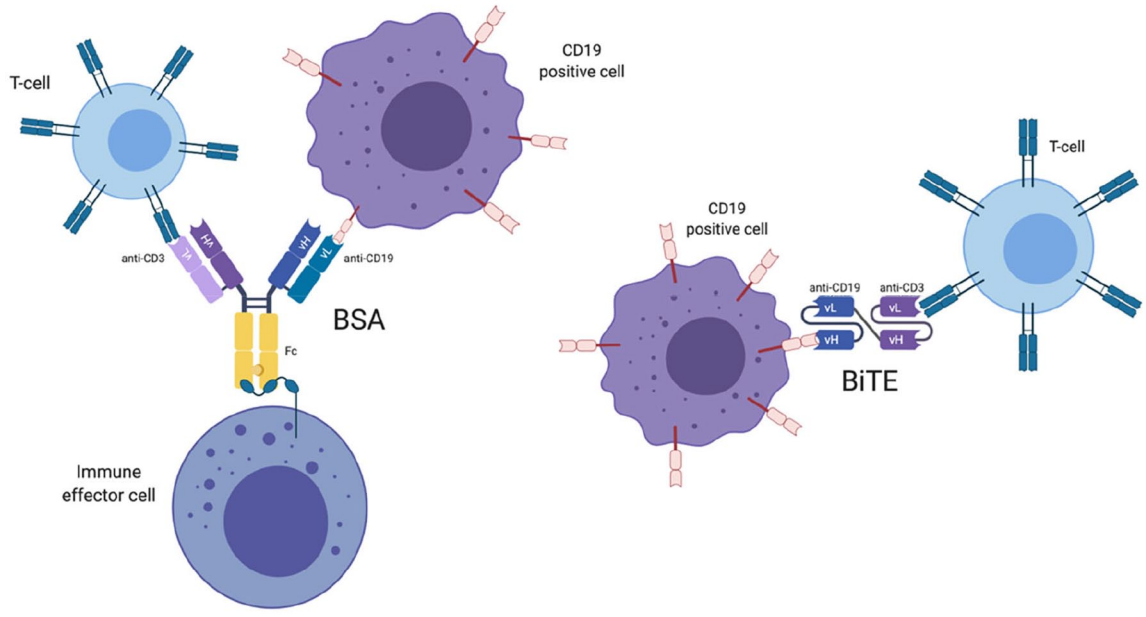

Figure 3. Bispecific antibodies comparison to Bispecific T-cell Engager. BiTEs target a tumour-specific antigen and CD3 which is present in T-cells 'bringing them' together and facilitating an immune response by the T-cell towards the tumour. BSAs work in a similar manner, but they also retain the Fc receptor which enables them to induce a broader immune response by other immune effector cells as well. Their larger size makes them less prone to renal excretion avoiding the need for a continuous infusion that BiTEs require.
BiTE, bi-specific T-cell engager; BSA, bispecific antibodies.

however, there is longer follow up data available for CAR-T cells allowing a degree of confidence that a significant number of patients enjoy durable remissions.[25] In addition, the responses appear to be similar for older patients (>65 years old) where other treatment options such as an autologous transplant may not be available.[46] While the BSA data is promising, longer follow up is required to determine the durability of remissions.

The future of the new therapies

R-CHOP has maintained its status as standard of care for the first line treatment of DLBCL for at least two decades. Despite many additional trials no other drug combination has so far been proven more efficacious or safer[42] {Nowakowski, 2021 #1655} {Bartlett, 2019 #1672}. However, with a CR rate of 70–80% there are some patients that could potentially benefit from newer drug developments. DLBCL is usually a type of lymphoma that presents aggressively and requires urgent treatment. R-CHOP is a regimen that can be given quickly and therefore it is likely that any new treatment will be used in combination with some of what constitutes R-CHOP. In addition, R-CHOP is a relatively inexpensive regimen that can be manufactured widely, while clinicians have vast amounts of experience using it to treat patients with B-cell malignancies.

Many of the 20% of patients who are primary-refractory to R-CHOP are double hit, or double-expressing lymphomas. For this category of patients, a more aggressive approach in the first-line setting by combining bispecific antibodies with R-CHOP or using R-CHOP as a bridge to CAR-T therapy may be a useful strategy; currently being investigated in the ZUMA-12 trial.[47] Initial results from this trial incorporating data from 12 patients show 80% CR rate with acceptable toxicity, but more results are awaited. In an elderly population with comorbidities, these treatments may become an attractive up-front alternative to cytotoxic chemotherapy.

A more feasible initial strategy is to use these therapies as second-line agents in the relapsed setting (Figure 3). Currently, second-line therapies have poor outcomes. Autologous stem cell

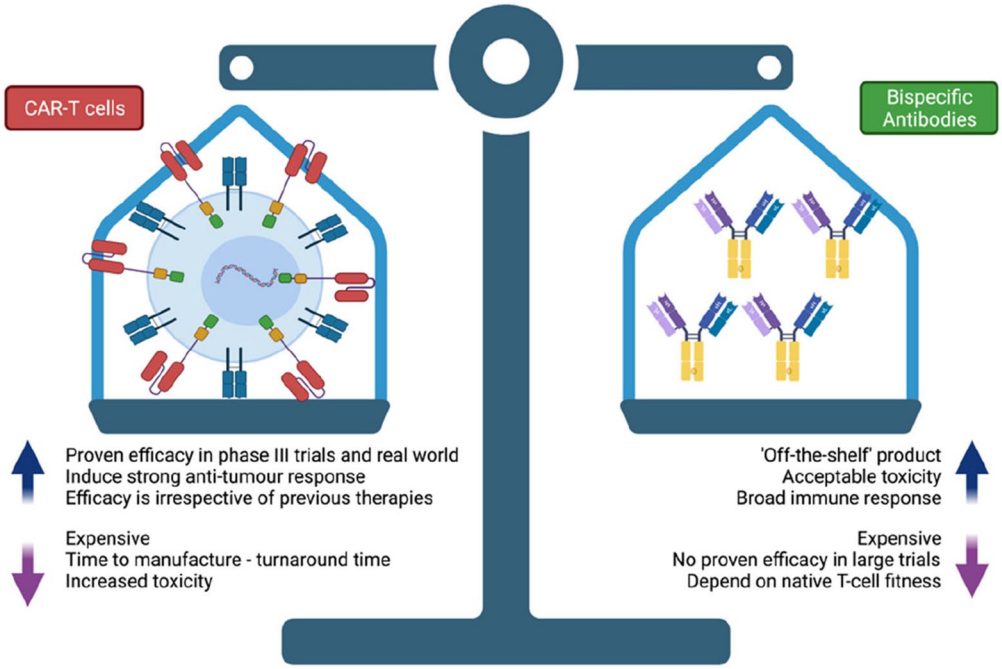

Figure 4. Benefits and limitations of CAR-T cells and bispecific antibodies.
CAR-T, chimeric antigen receptors-T cells.

transplantation can lead to durable remissions and cures for patients who remain chemosensitive at relapse and are young and fit enough to tolerate an intensive chemotherapy-based approach. In refractory cases or transplant-ineligible patients the overall prognosis remains poor with limited treatment options available. CAR-T cells have currently been approved in the United Kingdom in the third-line setting. There are two phase III trials currently active comparing CAR-T therapy to standard of care in R/R DLBCL following Rituximab plus Anthracycline-containing chemotherapy (NCT03391466, NCT03570892). Rates of grade 3 or higher neurotoxicity or CRS with CAR-T cells remain low with more than 50% of patients developing neither.[48] In the age group of above 70 years, where transplant would not usually be an option, CAR-T cells or BSAs offer an efficacious and tolerable alternative following R-CHOP failure. However, logistical and institutional challenges are significant hurdles to the wider adoption of CAR-T cells, while the associated toxicity and relatively long turnaround time may prevent some patients from having them, giving the advantage to 'off-the-shelf' BSAs. Other combination treatments with other novel agents such as Venetoclax have showed some positive initial results in phase I and are under investigation for this setting {Paolo Caimi, 2018 #1728}.

Challenges

Toxicity

CAR T-cell therapy is limited by toxicity mediated by the release of cytokines from activated immune cells (cytokine release syndrome, CRS) and neurotoxicity.[30] The management has become easier with use of specialized centres delivering therapy and clinical experience, but still remains a significant challenge. Long-term toxicity, including prolonged neutropenia, is being recognized as another notable adverse event. The mechanism for that remains elusive. Of note, B-cell aplasia and hypogammaglobinaemia are seen in much lower rates than in paediatric B-ALL. This may indicate the lack of persistence of CAR-T cells when used in DLBCL.

Cost

Perhaps the most significant problems limiting success in the scalability of autologous CAR T-cell therapies are the cost and manufacturing processes and facilities required to produce

patient-specific engineered cells. An estimated cost of US$400,000 per CAR-T treatment makes them extremely costly for wealthy nations and unreachable for the developing world.[49] A big part of this sum comes from the expensive manufacturing of viral vectors. However, the logistical difficulties of creating one product for one patient greatly inflates this cost. Commercialization of CAR T-cells is therefore limited by the availability of cost-effective GMP manufacturing platforms to produce treatments in a timely manner and at scale. Automated cell therapy production platforms such as CliniMACS Prodigy – an integrated cell processing device used to develop virus-specific T-cells, simplification and standardisation of quality control measures, and testing and tracking of products will allow for greater accessibility with reduction in costs.[50] The academic centres that use the CliniMACS Prodigy platform have been able to produce comparable products that are immediately available to their patients at a much lower price.[51] BSAs will likely be less expensive given their off-the-shelf nature, but judging by the Blinatumumab pricing of US$178,000 per year, they are likely to be far more expensive than conventional chemotherapy.

Availability

Another big hurdle with the use of CAR-T cells is the turnaround time between order and administration of treatment. Autologous CAR-Ts require T-cell apheresis and off-site manufacturing. The length of time taken from leukapheresis to reinfusion of the engineered product can often take multiple weeks, during which time a patient with relapsed/refractory disease may deteriorate and become too unwell for CAR T-cell treatment, given its toxicities. Even in trial settings, where turnaround time is much quicker and patients are generally fitter, around 10% of patients die while waiting to receive CAR therapy.[52,53] This number is likely to be much higher in the real world. Although the manufacturing process will hopefully become more efficient, it is unlikely that it will be reduced to less than 3–4 weeks. There have been a wide range of bridging therapies designed to help prevent rapid progression of lymphoma during CAR-T cell manufacturing, but there is no definitive evidence in terms of which therapy is better, while concerns about the effect on the fitness of CAR-T cells have been raised. There is emerging evidence that radiotherapy can be a very good bridging therapy, while also improving the efficacy and safety of CAR-T cells.[54]

Universal CAR-T

A universal, 'off-the-shelf', CAR T-cell will eliminate most of the delay in the manufacturing process and can potentially reduce the production cost. Attempts to mitigate the risk of graft versus host disease associated with allogenic cell therapies have included use of non-αβ T-cells such as NK cells or γδ T cells for generation of CAR T-cells, which have shown promise in the preclinical setting. No such products have been approved yet, but early phase clinical trials have proven that such an approach can potentially be effective.[55] Other than being easily available, this approach can go a long way towards addressing many of the current challenges with CAR-T cell therapy, while additionally providing an option for patients who do not achieve satisfactory T-cell apheresis due to previous lymphodepleted chemotherapies or impaired T-cell health. Cord-blood derived NK cells do not require HLA matching and so could be used as an off-the-shelf product.[56] Initial *in vitro* and murine models demonstrated their efficacy against CD19 malignancies[57] which led to the first product to be used in a human trial. It is engineered to express IL-15 to boost expansion and caspase 9 as an off-switch in the event of unacceptable toxicity alongside the anti-CD19 receptor. The first phase I/II trial of 11 patients has shown that CAR-NK cells are safe and efficacious in the management of CD19 positive malignancies.[46] Larger studies are in the pipeline to build upon this highly successful trial.

Conclusion

CAR-T therapy is an established therapy for R/R DLBCL, but improved cellular products with reduced toxicity, lower cost, and improved availability are the key to the wider adoption of this therapy. Upcoming trial results may indicate that they are the best option following R-CHOP, but the real-world large scale uptake would still be problematic if these challenges are not overcome. Bispecific antibodies offer a more 'off-the-shelf' solution and the results of larger phase II and phase III trials are awaited. They could be an addition to current regimens or an option for patients who have failed all other available treatments.

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Author contributions

All authors contributed equally to the writing of this manuscript.

Conflict of interest statement

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