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Review

T-cell-based Immunotherapies for Haematological Cancers, Part B: A SWOT Analysis of Adoptive Cell Therapies

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Abstract. *Haematology has been at the forefront of cancer immunotherapy advancements. Allogeneic haematopoietic stem cell transplant (allo-HSCT) is one of the earliest forms of cancer immunotherapy and continues to cure thousands of patients. Donor lymphocyte infusion (DLI) increases allo-HSCT efficacy and reduces graft-versus-host disease (GVHD). In recent years, chimeric antigen receptor (CAR)-T-cells have been approved for the treatment of distinct haematologic malignancies, producing durable response in otherwise untreatable patients. New target antigen identification and technological advances have enabled the structural and functional evolution of CARs, broadening their applications. Despite successes, adoptive T-cell (ATC) therapies are expensive, can cause severe adverse reactions and their use is restricted to few patients. This review considers the current status and future perspectives of allogeneic transplant and donor lymphocytes, as well as novel ATC therapies, such as CAR-T-cells in haematological malignancies by analysing their strengths, weaknesses, opportunities, and threats (SWOT). The biological rationale for anti-cancer mechanisms and development; current clinical data in specific haematological malignancies; efficacy, toxicity, response and resistance profiles; novel strategies to improve these characteristics; and potential targets to enhance or expand the application of these therapies are discussed.*

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Haematology boasts the first clinical application of one of the oldest forms of cancer immunotherapy: allogeneic hematopoietic stem cell transplantation. First performed in 1957, HSCT involves eradication of the patients' haematopoietic and immune system and replacement with donor stem cells. In 1968, E. Donnall Thomas performed pioneering work in allogeneic transplant, became the father of stem cell transplantation and won the Nobel Prize in Medicine and Physiology (1). Over one million HSCTs have been performed since, curing patients with haematologic malignancies, solid tumours, and non-cancerous diseases. HSCT remains the most frequently used cellular immunotherapy approach as its application continues to increase with widening of alternative donors and clinical indications (1-3).

In recent years, haematology has also been at the forefront of more novel T-cell-based immunotherapies. Tisagenlecleucel (Kymriah) was the first chimeric antigen receptor (CAR)-T-cell therapy approved in 2017 for the treatment of paediatric and young adults with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (BCP-ALL). Initial breakthroughs with CAR-T-cells spearheaded their application in other malignancies, including solid tumours, offering dramatic therapeutic potential in previously untreatable diseases.

Despite opportunities for cancer immunotherapies, several challenges remain. Limited applicability across diseases, unpredictable efficacy, and limiting toxicities attest to the need for further improvements. This review discusses the strengths, weaknesses, opportunities and threats (SWOT) associated with adoptive T-cell (ATC) therapies for haematological cancers including allogeneic transplant and donor lymphocytes, as well as novel ATC therapies outside the setting of allo-HSCT, with a focus on CAR-T-cells. The biological rationale for anti-cancer mechanism; clinical data in specific haematological cancers; efficacy, toxicity, response and resistance profiles; novel strategies to improve these characteristics; and potential targets to enhance or expand the application of these ATC therapies is discussed.

Allogeneic Haematopoietic Stem Cell Transplant (HSCT) and Donor Lymphocyte Infusion (DLI)

Biological rationale for anti-cancer mechanisms and development.

Allogeneic HSCT. Allo-HSCT involving transfer of genetically disparate (allogeneic) haematopoietic stem cells from healthy donors to patients is a widely used curative therapy in cancer and other diseases (4). The success of allo-HSCT derives from the ability to use intensive chemoradiotherapy and from donor-mediated graft-versus-tumour (GvT) immunity (5). However, a major limitation of allo-HSCT is graft-versus-host disease (GVHD), a systemic disorder characterised by donor graft T-cell immune reactivity against host allo-antigens. GVHD is a leading cause of transplant-related mortality. To reduce GVHD, strategies such as T-cell directed immunosuppression and allograft T-cell depletion have been employed. Benefits of donor graft T-cell depletion as a means to decrease chances of severe GVHD were realised early on (6-8). Yet, graft failure (9), disease relapse, and opportunistic infections necessitate improvement (10).

DLI. Donor lymphocyte infusion (DLI) from *ex vivo*-expanded allogeneic cytotoxic T lymphocytes reconstitutes immunity, thereby decreasing infection risk whilst increasing anti-tumour immune surveillance. DLI prevents cytomegalovirus reactivation (11) and treats post-transplant lymphoproliferative disease (PTLD) secondary to latent Epstein-Barr virus (EBV) reactivation (12). DLI has been employed against viral-related nasopharyngeal carcinoma and EBV^+ Hodgkin disease (13, 14). Donor T-cells also recognize non-self leukaemic cell antigens, eliminating them (10). In 1990, Kolb *et al.* showed that DLI could achieve disease remission following relapse after nonmyeloablative allogeneic transplant for chronic myelogenous leukaemia (CML) (15). DLI for relapse prevention has been investigated in multiple myeloma, acute leukaemias, and lymphomas (16-20). Today, DIL remains an important treatment, with refinements.

Clinical data reflecting current practice.

Allo-HSCT. According to the Centre for International Blood and Marrow Transplant Research (CIBMTR) (21), the number of allo-HSCTs in the USA increased by 1% in 2018, whereas autologous HSCTs decreased by 5%. Fewer autologous transplantations were performed for non-Hodgkin lymphoma (NHL), while haploidentical (mismatched) transplantations, a type of allo-HSCT using cells from a half-matched donor (typically a family member) increased. Post-transplantation cyclophosphamide prophylaxis for GVHD was undertaken in almost all haploidentical transplantations. Adults over 70 years old underwent HSCT at higher rates, particularly for acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS), for which allo-HSCT remains the most effective cellular immunotherapy (22) (Figure 1).

DLI refinements. DLI alloanergization by induction of hyporesponsive donor T-cell activity against recipient alloantigens facilitates autoimmune reconstitution while minimising GVHD. Alloanergization is achieved by recipient alloantigen presentation to donor T cells with concurrent costimulatory blockade to avoid alloantigen targeting. In a phase I study, low-dose alloanergized DLI following CD34-selected myeloablative haploidentical HSCT improved immune reconstitution without excess GVHD (22). Alternatively, DLI manipulation can involve elimination of GVHD-mediating T-cell populations. $CD8^+$ T-cell depletion was the first application. Others include CD25/Treg-depleted, CD4-depleted, and CD62L-depleted DLI (23-25).

Strengths of allo-HSCT and DLI.

Curative potential. Allo-HSCT offers curative potential in fatal diseases. The disease-free graft and immune-mediated GvT immunity from donor lymphocytes contribute to the treatment's success.

Limitations of allo-HSCT and DLI.

Human leukocyte antigen (HLA) restriction and GVHD. Despite advances with haploidentical HSCT, GVHD remains a serious cause of treatment failure and mortality. HLA restriction limits the possibility for universal off-the-shelf approaches.

Immunosuppression. Allo-HSCT requires systemic immunosuppression to prevent GVHD. Yet, immunosuppression limits the GvT immune response. Patients on long-term immunosuppression for chronic GVHD face toxicities and side effects. Tapering off immunosuppression risks GVHD, while immunotherapy resistance may occur in chronic GVHD (26).

Opportunities for allo-HSCT and DLI.

New therapeutic strategies. Prophylactic and therapeutic DLIs have been developed. Examples include combining pharmaceuticals with DLI, prior lymphodepletion, growth factor-primed DLI, and $CD4^+$ T-cell-enriched DLI. Prophylactic DLIs (pDLIs) include G-CSF-primed pDLIs and activated pDLIs (27).

Threats to allo-HSCT and DLI.

Novel ATC therapies, including CARs, offer durable responses without GVHD or immunosuppression since cells are autografted. Allogeneic CAR-T-cells are also possible if endogenous T-cell receptor (TCR) expression is disabled (preventing GVHD) and HLA matching is not required.

Adoptive T Cell Therapies Outside the Setting of Allo-HSCT

Biological rationale for anti-cancer mechanism and development.

TILs. The first ATC for non-viral cancers involved allogeneic transplant of tumour infiltrating lymphocytes (TILs) for leukaemia and melanoma. TILs are effector T-cells that infiltrate tumours, attacking cancer. In 1988, autologous TILs isolated from cancer biopsies and expanded with IL-2 before intravenous reinfusion into the same patient resulted in melanoma regression at a modest rate [34% overall response rate (ORR)]. However, median duration of response (DOR) was only 4-months (28, 29) due to immune tolerance and tumour escape.

TILs represent an experimental treatment, not used in routine clinical practice. Except for melanoma and cholangiocarcinoma, TILs have not been successful against other cancers as obtainment and sufficient expansion is challenging (30). TILs are limited by small numbers of invasive lymphocytes and lack of significant innate anti-tumour immunity enhancement (31).

Genetically engineered redirected T-cells overcome the limited T-cell migration and survival, and cancer immune escape associated with TILs (32, 33). Engineered T-cells express high affinity TCRs whereas natural T-cells with high-affinity TCRs are difficult to obtain, partly due to intra-thymic deletion (34).

Redirected T-cell therapy. Molecular identification of the TCR (35, 36) and the establishment of its role in antigen recognition (37, 38) laid the foundation for T-cell genetic engineering. T-cell engineering involves six steps: patient apheresis; T-cell enrichment; gene modification; activation and *ex vivo* expansion; quality control; and patient reinfusion (Figure 2). Modification of cytokine-encoding genes prolongs T-cell survival and cancer tissue penetration (32). Gene-editing strategies include retroviral vectors (39), liposomes (40), electroporation (41), and recently CRISPR/Cas9 (42-44).

TCR transgenic T-cells. Transferring cloned TCR genes from TILs to extracted patient T-cells was the first example of T-cell engineering (45, 46). Redirecting T-cells against cancer antigens has been shown to result in clinical regression (45, 47). Viral vector TCR-T-cell engineering to induce expression of CD20 has been found to be efficacious against NHL and mantle cell lymphoma (48) as well as in metastatic melanoma (49). TCR-T-cells against the cancer-testis antigens NY-ESO-1 and LAGE-1 demonstrated a response rate of 80% in multiple myeloma (MM) (50). Efficacy was also shown in neuroblastoma (51). Clinical trials are underway for haematological (52) and solid cancers (31). However, TCR transgenic T-cells have still not been approved. HLA and MHC-restriction, side effects, and lack of TCR genes with defined specificity (53, 54) have redirected interest towards CARs (55, 56).

CAR-T-cells. In the 1980s, T-cell specificity was redirected by incorporating genes encoding artificial TCR-like molecules formed by single-chain variable antibody fragments (scFv), spacers, transmembrane domains, and intracellular signalling components. These became known as chimeric antigen receptor (CAR)-T-cells (55, 56). CAR-T-cells target cancer surface antigens *via* scFv and exhibit MHC-independent cytotoxicity, thus broadening TCR applications (57). CAR-T-cells have evolved structurally and functionally (Figure 3) (58). Engineering involves electroporation or viral vectors (59). CAR-T-cells have been extensively investigated and have been shown to produce cytotoxicity (54-56, 60, 61) which results in dramatic control of haematological malignancies (62-65), with moderate efficacy against solid tumours (66-68). Four CAR-T-cell agents are licensed for haematologic malignancies.

Clinical translation.

Tisagenlecleucel (Kymriah®). Tisagenlecleucel was the first CAR-T therapy approved in August 2017 for relapse/refractory BCP-ALL (69). Tisagenlecleucel requires T-cell isolation and genetic modification of patient T-cells to express anti-CD19 CARs. The CAR protein features an extracellular murine anti-CD19 scFv portion and an intracellular T-cell signalling (CD3-ζ) and co-stimulatory (4-1BB) domain for T-cell activation, *in vivo* persistence and anti-tumour activity. A multicentre, open-label, single-arm trial of paediatric and young adult relapse/refractory BCP-ALL showed 83% ORR, 63% complete response (CR) and 19% CR with incomplete hematologic recovery (CRi) at 3 months. All responders were minimal residual disease negative (MRD <0.01%). Median CR DOR was not reached at 4.8 months (17% relapse). Grade 3-4 ARs included cytokine release syndrome (CRS) (49%), neurologic events (18%), febrile neutropenia (38%), prolonged cytopenias (37%), and infections (27%). Boxed warning and risk evaluation and mitigation strategy (REMS) were issued for CRS and neurotoxicity. Theoretically, tisagenlecleucel carries secondary malignancy risk by insertional or replication-competent lentivirus (RCL) mutagenesis. Tisagenlecleucel persisted *in vivo* up to 366 days after treatment. Apart from hypogammaglobulinemia due to on-target-off-tumour B-cell depletion no ARs persisted.

In May 2018 approval was expanded to adult relapse/refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, and follicular lymphoma (FL)-transformed DLBCL after two systemic therapies (70). In the single-arm, open-label, multicentre,

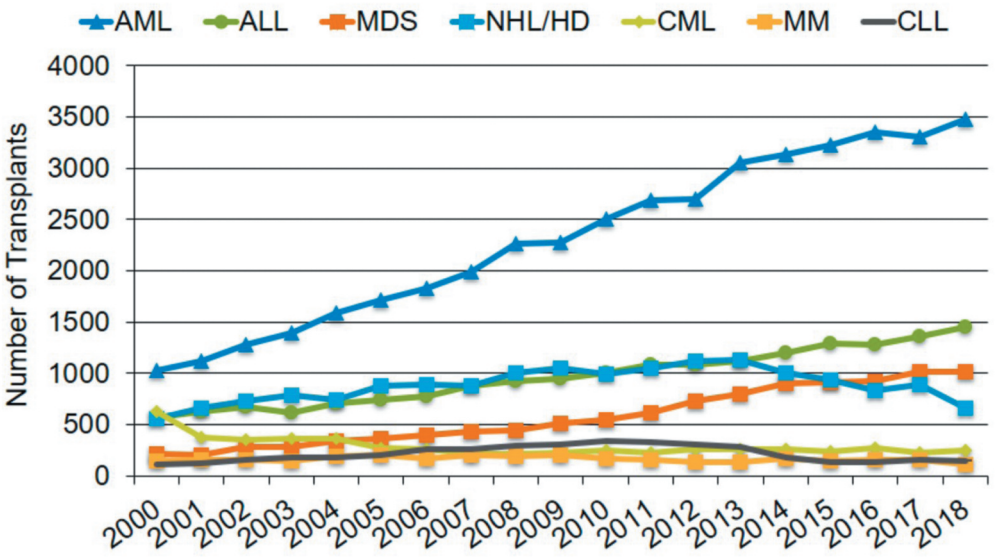

Figure 1. *Number of allogeneic transplants performed annually in the Unites States (US) among various disease indications. Allogeneic transplant activity is decreasing in a number of diseases including chronic leukemias, lymphomas, and multiple myeloma, likely due to the availability of newer non-allogeneic transplant options. Figure reproduced with permission from (21), data published from Centre for International Blood and Marrow Transplant Research (CIBMTR). AML: Acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; MDS: myelodysplastic syndrome; NHL: non-Hodgkin lymphoma; HL: Hodgkin's lymphoma; CML: chronic myeloid leukaemia; MM: multiple myeloma; CLL: chronic lymphocytic leukaemia.*

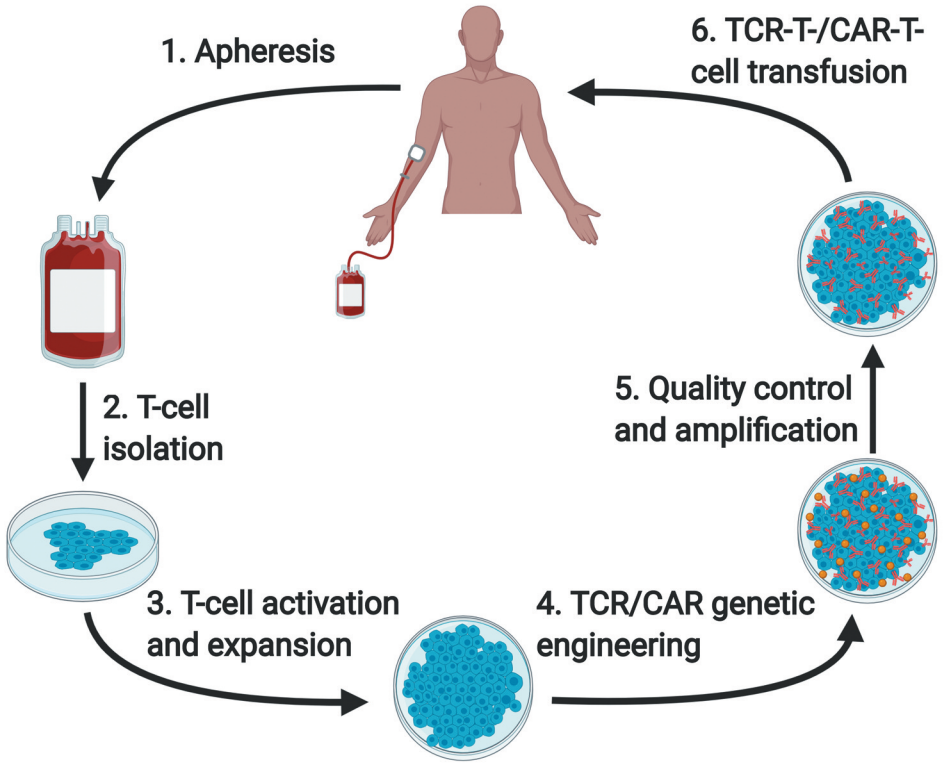

Figure 2. *Flow chart of the steps involved in engineered T-cell therapy. 1) Blood is drawn from patients to obtain sufficient numbers of peripheral blood mononuclear cells (PBMCs) for T-cell engineering. 2) T-cells are isolated from PBMCs and 3) are then activated and amplified in vitro. 4) T-cells are genetically engineered, for example, via transfection of a viral vector (lentivirus or retrovirus) to express specific CARs/TCRs on the cell surface. 5) T-cells are amplified and undergo quality control. Finally, 6) CAR-T- /TCR-T-cells are reinfused back into the patient to enhance antitumor immunity. Adapted from (31).*

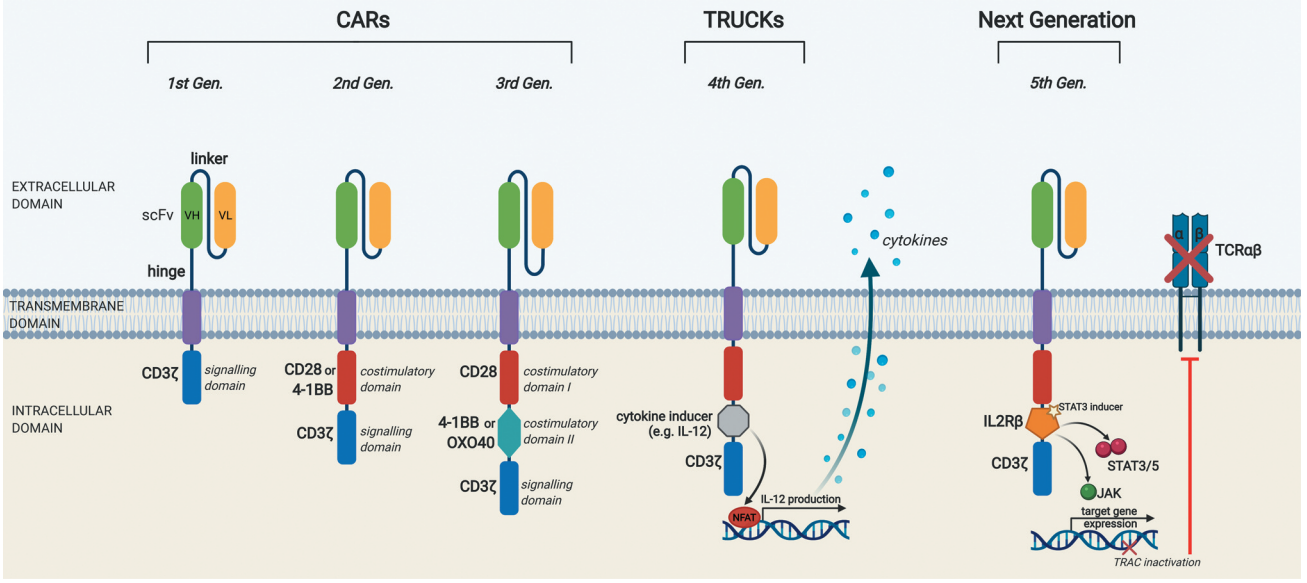

Figure 3. *Generations of CAR-T-cell construct designs. First generation CARs contained only the CD3ζ domain, the initiator of T-cell receptor intracellular signalling. However, these CARs demonstrated limited expansion and in vivo persistence due to lack of a costimulatory signal. Second generation CARs were engineered to contain CD3ζ and a co-stimulation signal such as CD28 or 4-1BB, thus conferring enhanced cytotoxicity, expansion, and persistence. Third generation CARs added another costimulatory domain with the first representing CD28 or 4-1BB and the second representing CD28, 4-1BB, or OXO40. These offer superior T-cell expansion and longer persistence through increased cytokine secretion, proliferation speed and survival rate of engrafted T cells. Fourth generation CARs, also called TRUCKs (T-cells redirected for universal cytokine-mediated killing), possess a cytokine induced domain which activates downstream transcription factor NFAT to induce cytokine production after antigen recognition, thus modulating immune effects. Fifth generation CARs, based on the second generation, require gene editing to inactivate the T-cell receptor alpha constant (TRAC) gene, leading to the removal of the TCR alpha and beta chains and the creation of a truncated cytoplasmic IL-2 receptor β-chain domain with a binding site for STAT3 transcription factor. Antigen activation triggers three synergistic signals through TCR CD3ζ, co-stimulatory CD28, and cytokine JAK–STAT3/5 signalling, which drive T-cell activation and proliferation (58). Adapted from (31).*

phase II study (71) patients received a single tisagenlecleucel infusion following lymphodepleting chemotherapy. ORR was 52% with 40% CR and 12% PR. At 12 months, 65% of responders experienced relapse-free survival (79% in CR patients). For CR patients, median DOR was not reached; for PR this was 3.4 months. Commonest grade 3-4 ARs included CRS (22%), neurologic events (12%), cytopenias (32%), infections (20%), and febrile neutropenia (14%). No deaths were caused by CRS or cerebral oedema. No difference in response based on CD19 tumour expression or immune checkpoint-related proteins were found.

Axicabtagene ciloleucel (Yescarta®). Axicabtagene ciloleucel (axi-cel), another autologous CD19-targeting CAR, gained FDA approval in October 2017 for adults with relapse/refractory large B-cell lymphoma, including DLBCL NOS, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma and DLBCL arising from FL, after two prior systemic therapies (72). Similarities to tisagenlecleucel include the murine anti-CD19 scFv and a CD3ζ intracellular signalling domain. However, axi-cel is linked to CD28 co-stimulatory domain and is created through retrovirus vector editing. Safety and efficacy were established in a phase II multicentre trial (73). CAR-T-cell administration after low-dose cyclophosphamide and fludarabine conditioning generated 82% ORR and 54% CR. Highly durable responses were reported with 52% 18-month overall survival (OS). Cytopenias were commonest grade 3-4 ARs. Grade 3-4 CRS (13%) and neurologic events (28%) resulted in the issue of Boxed Warning and REMS.

Brexucabtagene autoleucel (Tecartus™). Brexucabtagene autoleucel, another autologous CD19/CD28/CD3ζ gammaretroviral vector-transduced CAR, became the first CAR for mantle cell lymphoma (MCL). While structurally similar to axi-cel, manufacturing is different. Accelerated FDA approval was granted on July 2020 for adult relapse/refractory MCL (74) based on an open-label, multicenter, single-arm phase II trial (75). Patients received a single infusion of brexucabtagene autoleucel of 2×10^6 CAR-T cells per kilogram after leukapheresis and optional bridging therapy, followed by conditioning fludarabine and

cyclophosphamide lymphodepleting chemotherapy. Per-protocol analysis at 6 months showed 93% ORR with 67% CR while intention-to-treat analysis demonstrated 85% ORR with 59% CR. At 12.3-month median follow-up 57% were in remission. Progression-free survival (PFS) and OS at 12 months was 61% and 83%, respectively; median DOR was not reached. Commonest grade ≥3 ARs were cytopenias (94%) and infections (32%), while non-fatal CRS (15%) and neurological events (31%) resulted in issuing of REMS.

Belantamab mafodotin-blmf (Blenrep™). Belantamab mafodotin-blmf, the first anti-BCMA CAR, received accelerated FDA approval in August 2020, for adults with relapse/refractory MM after four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent (76). B-cell maturation antigen (BCMA) is an MM cell surface protein mediating plasma cell survival. The two-arm, randomised, open-label, multicentre phase 2 trial (77) evaluated blenrep at 2.5 mg/kg or 3.4 mg/kg infused intravenously over 30 minutes every 3 weeks until progressive disease or limiting toxicity. ORR was 31% with ≥6-month DOR in 73% of responders at 2.5 mg/kg. Boxed Warning was issued for corneal epithelium changes producing altered/blurred vision, loss of vision, corneal ulceration and dry eyes. Ocular toxicities restricted availability through BLENREP REMS. Ophthalmic exams at baseline, prior to each dose, and if symptoms worsen, are mandated.

Strengths of engineered T-cell therapies.
Responses in heavily pre-treated/resistant disease. CAR-T cells offer remarkable potential in heavily pre-treated and resistant disease. Approval for paediatric BCP-ALL and DLBCL, both highly aggressive diseases, is an important breakthrough.

Durable response and potential cure. Long-term response and survival information is limited. Ongoing CRs range between 43-113 months in aggressive lymphoma, low-grade lymphoma, and CLL treated with anti-CD19 CAR-T-cells offering hope for cure (78).

Flexibility. CAR synthesis with two receptors can refine specificity with "OR", "AND" and "NOT" Boolean logic gates (79). Additionally, disabling endogenous TCR expression allows for allogeneic CAR donors by preventing GVHD, rendering HLA matching unnecessary.

Limitations of engineered T-cell therapies.
Target antigen identification. Target antigen identification is not feasible for cancers without hallmark genetic phenotypes. High target expression in cancer and low expression in normal tissue reduces on-target off-tumour toxicities and maximises efficacy. Crossover targeting is only permissible without severe toxicity. Myelosuppression prevents myeloid malignancy CAR treatments since CD123 or CD33 are present on bone marrow stem cells (80). Antigen loss, such as in the case of CD19, may also induce treatment failure (81).

Toxicity. CRS, caused by strong *in vivo* proliferation, appears after cell transfer (82). Life-threatening effects involve hypotension, high fever, capillary leakage, coagulopathy and multiorgan failure (81). CAR-T-cell-related encephalopathy syndrome presents with confusion and delirium, sometimes seizures and cerebral oedema (83). First-line treatment for CRS and CAR-T-cell-related encephalopathy are glucocorticoids (81). Tocilizumab, a humanized anti-IL-6 antibody, is highly effective in second-line CRS treatment (84). Lymphopenia and hypogammaglobulinaemia (65), in CD19-specific CARs, are manageable with intravenous immunoglobulin (81).

Costs and availability. Engineered T-cells necessitate costly patient-specific design. Treatment access and manufacturing is limited (81, 85). Tisagenlecleucel and axicabtagene ciloleucel cost $475,000 and $373,000 per patient, respectively (81, 86), excluding expenses for severe ARs ($30,000) (86). ICIs cost $12,500 per month (81, 87). Despite restricted production to few centres, manufacturing variability and lack of standardisation produces heterogeneous outcomes (81, 85).

Manufacturing delay. Patient derived CAR manufacturing imposes a lengthy manufacturing time. Patients may relapse while waiting for treatment.

Opportunities for engineered T-cell therapies.
Other immune cells. Natural killer (NK) cells display GvT immunity without GVHD (88). Yet, tumour immune escape may emerge from cancer cell proteolytic shedding of immune-signalling ligands (89). Genetic deletion of immune checkpoints maintains NK activity, eliminating cancer more effectively than normal NKs. In phase I and II study, CD19 NK CARs achieved 75% ORR in relapse/refractory NHL and chronic lymphocytic leukaemia (CLL) without major toxicities (90).

New antigen targets. Target antigens are being evaluated in haematological and solid malignancies (91, 92). The orphan G protein-coupled receptor, class C group 5 member D (GPRC5D) antigen offers comparable *in vivo* efficacy and toxicity in BCMA (93). GPRC5D is also expressed on $CD138^+$ MM cells. Targeting CD22, expressed in B-ALL cancers, is a promising prospect currently under investigation in a phase I trial (94).

Improving efficacy. CARs revive exhausted T-cells and modulate inhospitable tumour microenvironment (TME) (81, 95, 96). New 'armoured' CAR-T-cells stimulate IL-12 production, overcoming Treg- and myeloid cell-mediated

immunosuppression, promoting $CD8^+$ T-cell activity (81, 97), and increasing myeloid cell recruitment and antigen presentation (81, 98, 99). In ovarian cancer models, IL-12-expressing-CARs against mucin 16 extracellular domain (MUC16ecto) were efficacious (81, 100, 101). A phase I trial in ovarian, fallopian or primary peritoneal cancer is ongoing (102). Chimeric cytokine receptor (4αβ) co-expression to stimulate IL-4-dependent cell proliferation enhances efficacy since IL-4 is abundant in the TME. This approach is effective across tumour-associated antigens (TAAs) (81, 103). Trials are ongoing for head and neck cancer (81, 104). Transcription factor JUN overexpression confers resistance to CAR-T-cell exhaustion, offering therapeutic potential (81, 105).

Reducing toxicity. IL-1 blockade is a novel intervention against CRS (81, 106). Low-affinity CD19-specific CAR-T-cells reduced toxicity and enhanced efficacy (107). CAR-T-cell engineering with multiple receptor specificities further reduces toxicity (81, 108). Transient receptor expression through mRNA-based methods (81, 109) and clonal deletion of infused cells by inclusion of a suicide cassette that is activated by exogenous agents (81, 110), reduces cellular toxicity half-life.

CAR-T-cell combination therapy with other immunotherapies. Combining CAR-T-cells with immunotherapies overcomes cancer-mediated immunosuppression. Anti-PD-1 agents enhance CAR-T efficacy, prolonging OS (111-114). In one case report of relapsed DLBCL following sole CAR-T-cell therapy in a patient with high PD-L1 expression, combination of CD19 CAR-T-cells with pembrolizumab achieved rapid remission, increased CAR-T-cell numbers, and decreased PD-1 expression (115). Oncolytic viruses may enhance CAR entry and mobilization through chemokines (116-118).

CAR-T-cell combination therapy with non-immuno-therapeutic modalities. Preclinical and clinical data support combinatorial chemotherapy with CAR-T-cells (119, 120). Chemotherapy improves CAR-T-cell efficacy reducing tumour burden and immunomodulation (120). Chemotherapy sensitises tumours to immunotherapy (121, 122), improves TAA presentation (123), inhibits immunosuppression (124), and inhibits autoimmunity prolonging CAR-T persistence *in vivo* (119, 125).

Radiotherapy improves CAR-T-cell efficacy, stimulating tumour-specific immunity to enhance tumour control locally and distantly (125-127). Local irradiation sensitises tumours to cytotoxic lymphocytes through TAA and MHCI expression (128). Radiotherapy stimulates cytokines, including IFN-γ, facilitating CAR-T-cell trafficking and TME infiltration (129), and improving TAA presentation (130).

There is limited evidence for chemo-radiotherapy (CRT) combination. CRT may increase CAR-T-cell efficacy by increasing T-cell density (131) and T-cell stimulation (132, 133). Further research should investigate CAR-T-cell combinations with non-immunotherapeutic treatments.

Threats to engineered T-cell therapies.
Although ATC therapies are at the forefront, ongoing breakthroughs may produce superior agents with improved on-target off-tumour toxicity, efficacy, response, and off-the-self availability. Examples of such agents include NK CARs.

Table I. *Summary of strengths weaknesses, opportunities and threats associated with allogeneic transplant and donor lymphocytes versus engineered adoptive T-cell therapies*.

	Allogeneic transplant & donor lymphocytes	Engineered adoptive T-cell therapies
Strengths	Curative potential	Responses in heavily pre-treated/resistant disease Durable response Potential for cure Flexibility
Weaknesses	HLA restriction and GVHD Immunosuppression	Target antigen identification Toxicity Costs and availability Manufacturing delay
Opportunities	New therapeutic strategies	Other immune cells New antigen targets Improving efficacy Reducing toxicity Combination therapy
Threats	Novel adoptive cell therapy agents (*e.g.*, CAR-T cells)	New superior adoptive cell therapy agents (*e.g.*, NK CARs)

Discussion

ATC therapies demonstrate outstanding therapeutic potential in haematological malignancies. Considering their strengths, weaknesses, opportunities and threats is essential to directing future investigation of their therapeutic potential (Table I).

Allo-HSCT and DLI are widely used immunotherapies that continue to cure many patients with haematological malignancies. However, HLA restriction, GVHD and immunosuppression have contributed to their overshadowing by novel ATC agents, which may even allow for allogeneic donors and HLA-independence by disabling endogenous TCR expression. Nevertheless, allo-HSCT and novel strategies for DLI modifications are still widely investigated.

Novel ATC therapies have produced remarkable responses in patients. However, they involve costly development of a new therapeutic agent that is unique for each patient, while T-cells take weeks to culture and patients require considerable hospitalisation to receive treatment (134). MHC restriction and the specificity of genomic aberrations to the cancer being targeted prevent individual-synthesised ATC therapies from being expanded across the general population, unlike agents such as immune checkpoint inhibitors and bispecific T-cell engagers which are broad-based, cost-effective, off-the-shelf agents.

Conclusion

ATC therapies are a powerful therapeutic option for heavily treated, otherwise non-responsive patients and non-immunogenic cancers, which thus far represent the overwhelming majority of human malignancies. Although challenges persist, technological advances and novel strategies to improve efficacy, reduce toxicity, and broaden the application of ATC therapies are set to revolutionise the landscape of cancer treatment in upcoming years.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

K.S.R. has contributed to reviewing the literature, drafting and revising the article, figure illustrations, and final approval of the review. C.H. has contributed to revising the article and final approval of the article. M.S. has contributed to revising the article and final approval of the article. J.K.D. has contributed to the conceptualization of the work, revising the article, supervising the work, and final approval of the article.

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