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

KATHRINE S. RALLIS1,2, CHRISTOPHER R.T. HILLYAR2, MICHAIL SIDERIS3 and JEFF K. DAVIES1

1Barts Cancer Institute, Queen Mary University of London, London, U.K.; 2Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, U.K.; 3Women’s Health Research Unit, Queen Mary University of London, London, U.K.

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 untreated 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.

This article is freely accessible online.

Correspondence to: Kathrine S. Rallis, MSc, Barts and The London School of Medicine and Dentistry, Turner Street, Whitechapel, London E1 2AD, U.K. Tel: +44 2078822239, +44 7546272233, e-mail: k.s.rallis@smd16.qmul.ac.uk

Key Words: Hematologic malignancies, T cells, T-cell immunotherapy, cancer immunotherapy, adoptive cell therapy, haematopoietic stem cell transplant, donor lymphocyte infusion (DLI) chimeric antigen receptor (CAR)-T-cells, cancer treatment, review.

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 untreated 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 hypo-responsive 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 DLI’s have been developed. Examples include combining pharmaceuticals with DLI, prior lymphodepletion, growth factor-primed DLI, and CD4+ T-cell-enriched DLI. Prophylactic DLI’s (pDLI) include G-CSF-primed pDLI’s and activated pDLI’s (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 attainment 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 intrathymic 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 cytophenias (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 United 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).
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 cileoceleucel (Yescarta®). Axicabtagene cileoceleucel (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 2×10⁶ 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 CD19+ 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-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                   | Target antigen identification        |
|                                | Immunosuppression                          | 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. J.K.D. has contributed to reviewing the article, figure illustrations, and final approval of the article. M.S. has contributed to revising the article and final approval of the article. C.H. has contributed to revising the article and final approval of the article. J.K.D. has contributed to revising the article, figure illustrations, and final approval of the article.

Acknowledgements

Figures were created with BioRender.com. Figure 1 was reproduced with permission from (21). Figure 1 data published from the Centre for International Blood and Marrow Transplant Research (CIBMTR). Figures 2 and 3 were adapted from (31), published under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

1. Im A and Pavletic SZ: Immunotherapy in hematologic malignancies: past, present, and future. J Hematol Oncol 10: 94, 2017. DOI: 10.1186/s13045-017-0453-8
2. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, Rimm AA, Rindéon O, Rozman C and Speck B: Graft-versus-leukemia reactions after bone marrow transplantation. Blood 75: 555-562, 1990. PMID: 2297567.
3. Weiden PL, Flountoy N, Thomas ED, Prentice R, Fefer A, Buckley CD and Storb R: Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N Engl J Med 300: 1068-1073, 1979. PMID: 34792. DOI: 10.1056/NEJM197905103001902
4. Henig I and Zuckerman T: Hematopoietic stem cell transplantation—50 years of evolution and future perspectives. Rambam Maimonides Med J 5, 2014. PMID: 25386344. DOI: 10.5041/RMMJ.10162
5. Singh AK and McGuirk JP: Allogeneic stem cell transplantation: a historical and scientific overview. Cancer Res 76: 6445-6451, 2016. PMID: 27784742. DOI: 10.1158/0008-5472.CAN-16-1311
6. Champlin RE, Mitsuyasu RT and Gale RP: Transplantation of T lymphocyte depleted bone marrow to prevent graft-versus-host disease: its implications for fetal liver transplantation. Prog Clin Biol Res 193: 315-325, 1985. PMID: 3911215.
7. Löwenberg B, Wagemaker G, van Bekkum DW, Sizoo W, Sintnicolaas K, Hendriks WD and Hagenbeek A: Graft-versus-host disease following transplantation of “one log” versus “two log” T-lymphocyte-depleted bone marrow from HLA-identical donors. Bone Marrow Transplant 1: 133-140, 1986. PMID: 3332128.
8. Patterson J, Prentice HG, Brenner MK, Gilmore M, Janossy G, Ivory K, Stagg D, Morgan H, Lord J and Blacklock HA: Graft rejection following HLA matched T-lymphocyte depleted bone marrow transplantation. Br J Haematol 63: 221-230, 1986. PMID: 3521712. DOI: 10.1111/j.1365-2141.1986.tb05544.x
9. Apperley JF, Jones L, Hale G, Waldmann H, Hows J, Rombos Y, Tsatalas C, Marcus RE, Goolden AW and Gordon-Smith EC: Bone marrow transplantation for patients with chronic myeloid leukaemia: T-cell depletion with Campath-1 reduces the incidence of graft-vs-host-disease but may increase the risk of leukaemic relapse. Bone Marrow Transplant 1: 53-66, 1986. PMID: 3332120.
10. Deol A and Lum LG: Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited. Cancer Treat Rev 36: 528-538, 2010. PMID: 20381970. DOI: 10.1016/j.ctrv.2010.03.004
11. Riddell SR, Watanabe KS, Goodrich JM, Li CR, Agha ME and Greenberg PD: Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. Science 257: 238-241, 1992. PMID: 1352912. DOI: 10.1126/science.1352912
12. Papadopoulos EB, Ladanyi M, Emanuel D, Mackinnon S, Boulad F, Carabasi MH, Castro-Malaspina H, Childs BH, Gillio AP and Small TN: Infusions of donor leukocytes to treat Epstein-Barr virus-associated lymphoproliferative disorders after allogeneic
bone marrow transplantation. N Engl J Med 330: 1185-1191, 1994. PMID: 8093146. DOI: 10.1056/NEJM199404283301703
13 Bollard CM, Aguilar L, Straathof KC, Gahn B, Huls MH, Rousseau A, Sixby J, Greisik MV, Carrum G, Hudson M, Dilloo D, Gee A, Brenner MK, Rooney CM and Heslop HE: Cytoxic T lymphocyte therapy for Epstein-Barr virus+ Hodgkin’s disease. J Exp Med 206: 1623-1633, 2004. PMID: 15611290. DOI: 10.1084/jem.20040890
14 Louis CU, Straathof K, Bollard CM, Gerken C, Huls MH, Greisik MV, Wu M-F, Weiss HL, Gee AP, Brenner MK, Rooney CM, Heslop HE and Gottschalk S: Enhancing the in vivo expansion of adoptively transferred EBV-specific CTL with lymphodepleting CD45 monoclonal antibodies in NPC patients. Blood 113: 2442-2450, 2009. PMID: 18971421. DOI: 10.1182/blood-2008-05-157222
15 Kolb HJ, Mittermüller J, Clemm C, Holler E, Ledderose G, Brehm G, Heim M and Wilmanns W: Donor leukocyte transusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 76: 2462-2465, 1990. PMID: 2265242. DOI: 10.1182/blood.V76.12.2462
16 Salama M, Nevill T, Marcellus D, Parker P, Johnson M, Kirk A, Porter D, Girali S, Levine JE, Drobsky W, Barrett AJ, Horowitz M and Collins RH: Donor leukocyte infusions for multiple myeloma. Bone Marrow Transplant 26: 1179-1184, 2000. PMID: 11149728. DOI: 10.1038/sj.bmt.1702685
17 van der Griend R, Verdonck LF, Petersen EJ, Veenhuizen P, Bloem AC and Lokhorst HM: Donor leukocyte infusions inducing remissions repeatedly in a patient with recurrent multiple myeloma after allogeneic bone marrow transplantation. Bone Marrow Transplantation 23: 195-197, 1999. PMID: 10197809. DOI: 10.1038/sj.bmt.1701546
18 Verdonck LF, Petersen EJ, Lokhorst HM, Nieuwenhuis HK, Dekker AW, Tilanus MG and de Weger RA: Donor leukocyte infusions for recurrent hematologic malignancies after allogeneic bone marrow transplantation: impact of infused and residual donor T cells. Bone Marrow Transplant 22: 1057-1063, 1998. PMID: 9877267. DOI: 10.1038/sj.bmt.1701496
19 Schapa N, Schattenberg A, Bär B, Preijers F, van de Wiel van Kemenade E and de Witte T: Induction of graft-versus-leukemia to prevent relapse after partially lymphocyte-depleted allogeneic bone marrow transplantation by pre-empitive donor leukocyte infusions. Leukemia 15: 1339-1346, 2001. PMID: 11516094. DOI: 10.1038/sj.leu.2402203
20 Lokhorst HM, Schattenberg A, Cornelissen JI, Thomas LL and Verdonck LF: Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. Blood 90: 4206-4211, 1997. PMID: 9354693. DOI: 10.1182/blood.V90.10.4206
21 D’Souza A, Fretham C, Lee SJ, Arora M, Brunner J, Chhabra S, Devine S, Eapen M, Hamadani M, Hari P, Pasquinii MC, Perez W, Phelan RA, Riches ML, Rizzo JD, Saber W, Shaw BE, Spellman SR, Steinhart P, Weidsoeld DJ and Horowitz MM: Current use of and trends in hematopoietic cell transplantation in the united states. Biol Blood Marrow Transplant J 26: e177-e182, 2020. PMID: 32438042. DOI: 10.1016/j.bbmt.2020.04.013
22 Davies JK, Brennan LL, Wingard JR, Cogle CR, Kapoor N, Shah AJ, Dey BR, Spitzer TR, de Lima M, Cooper LJ, Thall PF, Champlin RE, Nadler LM and Guinan EC: Infusion of alloengenerated donor lymphocytes after CD34-selected haploidentical hematopoietic stem cell transplantation. Clin Cancer Res 24: 4098-4109, 2018. DOI: 10.1158/1078-0432.CCR-18-0449
23 Shi M, Li M, Cui Y, Liu L, Adachi Y and Ikehara S: CD4+ T cell-depleted lymphocyte infusion impairs neither the recovery of recipient thymus nor the development of transplanted thymus. J Immunol 190: 2976-2983, 2013. PMID: 23382561. DOI: 10.4049/jimmunol.1201605
24 Nikiforow S, Kim HT, Daley H, Reynolds C, Jones KT, Armand P, Ho VT, Aileya EP, Cutler CS, Ritz J, Antin JH, Soiffer RJ and Koreth J: A phase I study of CD25/regulated T-cell-depleted donor lymphocyte infusion for relapse after allogeneic stem cell transplantation. Haematologica 101: 1251-1259, 2016. PMID: 27354021. DOI: 10.3324/haematol.2015.141176
25 Verfuert S, Sousa PSE, Beloki L, Murray M, Peters MD, Mackinnon S, Lowdell MW, Chakraverty R and Samuel ER: Generation of memory T cells for adoptive transfer using clinical-grade anti-CD62L magnetic beads. Bone Marrow Transplant 50: 1358-1364, 2015. DOI: 10.1038/bmt.2015.13
26 Bouchlaka MN, Redelman D and Murphy WJ: Immunotherapy following hematopoietic stem cell transplantation: potential for synergistic effects. Immunotherapy 2: 399-418, 2010. PMID: 20635904. DOI: 10.2217/imt.10.20
27 Chang X, Zang X and Xia CQ: New strategies of DLI in the management of relapse of hematological malignancies after allogeneic hematopoietic SCT. Bone Marrow Transplant 31: 324-332, 2016. DOI: 10.1038/bmt.2015.288
28 Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, Simon P, Lotze MT, Yang JC and Seipp CA: Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med 319: 1676-1680, 1988. PMID: 3264384. DOI: 10.1056/NEJM198812223192527
29 Rosenberg SA, Yannelli JR, Yang JC, Topalian SL, Schwartzentuber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH and White DE: Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med 319: 1676-1680, 1988. PMID: 3264384. DOI: 10.1056/NEJM198812223192527
30 Li D, Li X, Zhou W-L, Huang Y, Liang X, Jiang X, Sun J, Li Z, Han W-D and Wang W: Genetically engineered T cells for cancer immunotherapy. Signal Transduct Target Ther 4: 1-17, 2019. DOI: 10.1038/s41392-019-0070-9
31 Zhao L and Cao YJ: Engineered T cell therapy for cancer in the clinic. Front Immunol 10, 2019. PMID: 31681259. DOI: 10.3389/fimmu.2019.02250
32 Kershaw MH, Westwood JA and Darcy PK: Gene-engineered T cells for cancer therapy. Nat Rev Cancer 13: 525-541, 2013. PMID: 23880905. DOI: 10.1038/nrc3565
33 Sadelain M, Riviere I and Riddell S: Therapeutic T cell engineering. Nature 545: 423-431, 2017. PMID: 28541315. DOI: 10.1038/nature22395
34 Gattinoni L, Powell DJ, Rosenberg SA and Restifo NP: Adoptive immunotherapy for cancer: building on success. Nat Rev Immunol 6: 383-393, 2006. DOI: 10.1038/nri1842
35 Hedrick SM, Cohen DJ, Nielsen EA and Davis MM: Isolation of cDNA clones encoding T cell-specific membrane-associated proteins. Nature 308: 149-153, 1984. PMID: 6199676. DOI: 10.1038/308149a0
36 Yanagi Y, Yoshikai Y, Leggett K, Clark SP, Aleksander I and Mak TW: A human T cell-specific cDNA clone encodes a protein
FDA approval brings first gene therapy to treat adults with certain types of large B-cell lymphoma. FDA, 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-to-treat-adults-with-certain-types-large-b-cell-lymphoma [Last accessed on August 12, 2020]

Bouchkouj N, Kasamon YL, Claro RA de, George B, Lin X, Lee S, Blumenthal GM, Bryan W, McKee AE and Pazdur R: FDA Approval Summary: axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma. Clin Cancer Res 25: 1702-1708, 2019. PMID: 30413526. DOI: 10.1158/1078-0432.CCR-18-2743

FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma. FDA, 2020. Available at: https://www.fda.gov/drugs/fda-approves-brexucabtagene-autoleucel-relapsed-or-refractory-mantle-cell-lymphoma#:~:text=On%20July%2024%2C%202020%2C%20the,mantle%20cell%20lymphoma%20(MCL) [Last accessed on August 12, 2020]

Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, Timmerman JM, Holmes H, Jaglowski S, Flinn IW, McSweeney PA, Miklos DB, Pagel JM, Kersten M-J, Milipied N, Fung H, Topp MS, Houtot R, Beatijn A, Peng W, Zheng L, Rossi JM, Jain RK, Rao AV and Reagan PM: KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med 382: 1331-1342, 2020. PMID: 32243538. DOI: 10.1056/NEJMoa1914347

Research C for DE and: FDA granted accelerated approval to belantamab mafodotin-blmf for multiple myeloma. FDA, 2020.

Lonsal S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, Abdallah A-O, Callander N, Lendvai N, Sborov D, Suvannasankha A, Weisel K, Karlin L, Libby E, Arnulf B, Facon T, Hulin C, Korttum KM, Rodriguez-Otero P, Usmani SZ, Hari P, Baz R, Quach H, Moreau P, Voorhees PM, Gupta I, Hoos A, Zhi E, Baron J, Pintek T, Lewis E, Jewell RC, Dettman EJ, Popat R, Esposti SD, Opalinska J, Richardson P and Cohen AD: Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 21: 207-221, 2020. PMID: 31859245. DOI: 10.1016/S1470-2045(19)30788-8

Cappell K, Sherry RM, Yang JC, Goff SL, Vanasse D, McIntyre L, Rosenberg SA and Kochenderfer JN: Long-term follow-up of anti-CD19 CAR T-cell therapy for B-cell lymphoma and chronic lymphocytic leukaemia. J Clin Oncol 38: 3012-3012, 2020. DOI: 10.1200/JCO.2020.38.15_suppl.3012

Han X, Wang Y, Wei J and Han W: Multi-antigen-targeted chimeric antigen receptor T cells for cancer therapy. J Hematol Oncol 12: 128, 2019. PMID: 31783889. DOI: 10.1186/s13045-019-0813-7

Huang R, Li X, He Y, Zhu W, Gao L, Liu Y, Gao L, Wen Q, Zhong JF, Zhang C and Zhang X: Recent advances in CAR-T cell engineering. J Hematol Oncol 13: 86, 2020. DOI: 10.1186/s13045-020-00910-5

Waldman AD, Fritz JM and Lenardo MJ: A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol, 2020. DOI: 10.1038/s41577-020-0306-0

Leeplap S, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, Komanduri KV, Lin Y, Jain N, Daver N, Westin J, Gulbis AM, Loghin ME, de Groot JF, Adkins S, Davis SE, Rezvani K, Hwu P and Shpall EJ: Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 15: 47-62, 2018. PMID: 28925994. DOI: 10.1038/nrc Cancer.2017.148
83 Brudno JN and Kochenderfer JN: Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 127: 3321-3330, 2016. PMID: 27207799. DOI: 10.1182/blood-2016-04-703751

84 Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B and von Bergwelt-Baildon MS: Cytokine release syndrome. J Immunother Cancer 6: 56, 2018. PMID: 29907163. DOI: 10.1186/s41445-018-0343-9

85 Vormmittag P, Gunn R, Ghorashian S and Veraitch FS: A guide to manufacturing CAR T cell therapies. Curr Opin Biotechnol 53: 164-181, 2018. PMID: 29462761. DOI: 10.1016/j.copbio.2018.01.025

86 Hernandez I, Prasad V and Gellad WF: Total costs of chimeric antigen receptor T-cell immunotherapy. JAMA Oncol 4: 994-996, 2018. PMID: 29710129. DOI: 10.1001/jamaoncol.2018.0977

87 Moon EK, Langer CJ and Albelda SM: The era of checkpoint blockade in lung cancer: taking the brakes off the immune system. Ann Am Thorac Soc 14: 1248-1260, 2017. PMID: 28613923. DOI: 10.15115/AnnalsATS.201702-152F

88 Habib S, Tariq SM and Tariq M: Chimeric antigen receptor-natural killer cells: the future of cancer immunotherapy, Ochsner J 19: 186-187, 2019. PMID: 31528126. DOI: 10.3148/toj.19.0033

89 Holdenrieder S, Eichhorn P, Beuers U, Samtleben W, Steiber P, Nagel D, Peterfi A, Steinle A and Salih HR: Soluble NKG2D ligands in hepatic autoimmune diseases and in benign diseases involved in marker metabolism. Anticancer Res 27: 2041-2045, 2007. PMID: 17649819.

90 Liu E, Marin D, Banerjee P, Macapinlac HA, Thompson P, Basar R, Kerbauy LN, Overman B, Thall P, Kaplan M, Nandivada V, Kaur J, Cortes AN, Cao K, Daher M, Hosing C, Cohen EN, Kebraipei P, Mehta R, Neelapu S, Nieto Y, Wang M, Wierda W, Keating M, Champin R, Shpall EJ and Rezvani K: Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. Sci Transl Med 11: 250ra95, 2019. PMID: 30918115. DOI: 10.1126/scitranslmed.aau7746

91 Jackson HJ, Rafiq S and Brentjens RJ: Driving CAR T-cells forward. Nat Rev Clin Oncol 13: 370-383, 2016. PMID: 27000958. DOI: 10.1038/nrclinonc.2016.36

92 Smith EL, Harrington K, Staehr M, Masakayan R, Jones J, Long TJ, Ng KY, Ghodssi M, Purdon TJ, Wang X, Do T, Pham MT, Brown JM, De Larrea CF, Olson E, Peguero E, Wang P, Liu H, Xu Y, Garrett-Thomson SC, Almo SC, Wendel H-G, Riviere I, Liu C, Sather B and Brentjens RJ: GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. Sci Transl Med 11, 2019. PMID: 30918115. DOI: 10.1126/scitranslmed.aau7746

93 Fry TJ, Shah NN, Orenats RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, Wolters P, Martin S, Delbrook C, Yates B, Shalabi H, Fountaine TJ, Sern JF, Majzner RG, Songce DF, Sabatino M, Feng Y, Dimitrov DS, Zhang L, Nguyen S, Qin H, Dropulic B, Lee DW and Mackall CL: CD222-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 24: 20-28, 2018. PMID: 29155426. DOI: 10.1038/nm.4441

94 Batchu RB, Grudzyn OV, Mahmud EM, Chukr F, Dachepalli R, Mammar SK, Mostafa G, Weaver DW and Gruber SA: Inhibition of Interleukin-10 in the tumor microenvironment can restore mesothelin chimeric antigen receptor T cell activity in pancreatic cancer in vitro. Surgery 163: 627-632, 2018. PMID: 29336814. DOI: 10.1016/j.surg.2017.10.050

95 Chang ZL, Lorenzini MH, Chen X, Tran U, Bangayan NJ and Chen YY: Rewiring T-cell responses to soluble factors with chimeric antigen receptors. Nat Chem Biol 14: 317-324, 2018. PMID: 29377003. DOI: 10.1038/nchembio.2565

96 Zhao J, Zhao J and Perlman S: Differential effects of IL-12 on Tregs and non-Treg T cells: roles of IFN-γ, IL-2 and IL-2R. PloS One 7: e46241, 2012. PMID: 23029447. DOI: 10.1371/journal.pone.0046241

97 Kerkar SP, Goldszmid RS, Muranski P, Chinnasamy D, Yu Z, Reger RN, Leonard AJ, Morgan RA, Wang E, Marincola FM, Trinchieri G, Rosenberg SA and Restifo NP: IL-12 triggers a programmatic change in dysfunctional myeloid-derived cells within mouse tumors. J Clin Invest 121: 4746-4757, 2011. PMID: 22056381. DOI: 10.1172/JCI58814

98 Zmielewski M, Kopecky C, Hombach AA and Abken H: IL-12 release by engineered T cells expressing chimeric antigen receptors can effectively muster an antigen-independent macrophage response on tumor cells that have shut down tumor antigen expression. Cancer Res 75: 5697-5706, 2011. PMID: 21742772. DOI: 10.1158/0008-5472.CAN-11-0103

99 Yeku OO, Purdon TJ, Koneru M, Spriggs D and Brentjens RJ: Armored CAR T cells enhance antitumor efficacy and overcome the tumor microenvironment. Sci Rep 7: 10541, 2017. PMID: 28874817. DOI: 10.1038/s41591-017-10940-8

100 Koneru M, Purdon TJ, Spriggs D, Koneru S and Brentjens RJ: IL-12 secreting tumor-targeted chimeric antigen receptor T cells eradicate ovarian tumors in vivo. Oncoimmunology 4: e994446, 2015. PMID: 25949921. DOI: 10.4161/2162402X.2014.994446

101 Koneru M, O’Cearbhaill R, Pendharkar S, Spriggs DR and Brentjens RJ: A phase I clinical trial of adoptive T cell therapy using IL-12 secreting MUC-16(ecto) directed chimeric antigen receptors for recurrent ovarian cancer. J Transl Med 13: 102, 2015. PMID: 25890361. DOI: 10.1186/s12967-015-0460-x

102 Wilkie S, Burbridge SE, Chiapero-Stanke L, Pereira AC, Cleary S, van der Stegen SJC, Spencer JP, Davies DM and Maher J: Selective expansion of chimeric antigen receptor-targeted T-cells with potent effector function using interleukin-4. J Biol Chem 285: 25538-25544, 2010. PMID: 20562098. DOI: 10.1074/jbc.M110.127951

103 van Schalkwyk MCI, Papa SE, Jeannon J-P, Guerrero Urbano T, Spencer JP and Maher J: Design of a phase I clinical trial to evaluate intratumoral delivery of ErbB-targeted chimeric antigen receptor T-cells in locally advanced or recurrent head and neck cancer. Hum Gene Ther Clin Dev 24: 134-142, 2013. PMID: 24099518. DOI: 10.1089/humc.2013.144

104 Lynn RC, Weber EW, Sotillo E, Gennert D, Xu P, Good Z, Anbusathan H, Lattin J, Jones R, Tieu V, Nagaraja S, Granja J, de Bourcy CFA, Majzner R, Satpathy AT, Quake SR, Monje M, Chang HY and Mackall CL: c-Jun overexpression in CAR T cells induces exhaustion resistance. Nature 576: 293-300, 2019. PMID: 31802004. DOI: 10.1038/s41586-019-1805-z

105 Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Pierisgill A and Sadclain M: CAR T cell-generated cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 24: 731-738, 2018. PMID: 29808005. DOI: 10.1038/s41591-018-0041-7
107 Ghorashian S, Kramer AM, Onouha S, Wright G, Bartram J, Richardson R, Albon SJ, Casanova-Company J, Castro F, Popova B, Villanueva K, Yeung J, Vetharyo W, Guvenel A, Wawrzyniecka PA, Mekkaoui L, Cheung GW-K, Pinner D, Chu J, Lucchin G, Silva J, Ciocarlie O, Lazareva A, Inglott S, Gilmour KC, Ahsan G, Ferrari M, Manzoor S, Champion K, Brooks T, Lopes A, Hackshaw A, Farzanefar F, Chiesa R, Rao K, Bonney D, Samarasinghe S, Goulden N, Vora A, Veys P, Hough R, Wynn R, Pule MA and Amrolia PJ: Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med 25: 1408-1414, 2019. PMID: 31479906. DOI: 10.1038/s41591-019-0549-5

108 Bielamowicz K, Fousek K, Byrd TT, Samaha H, Mukherjee M, Aware N, Wu M-F, Orange JS, Sumazin P, Man T-K, Joseph SK, Hegde M and Ahmed N: Trivalent CAR T cells overcome interpatient antigenic variability in glioblastoma. Neuro Oncol 20: 506-518, 2018. PMID: 29016929. DOI: 10.1093/neo/nox182

109 Hung C-F, Xu X, Li L, Ma Y, Jin Q, Viley A, Allen C, Natarajan P, Shivakumar R, Peshwa MV and Emens LA: Development of anti-human mesothelin-targeted chimeric antigen receptor messenger RNA-transfected peripheral blood lymphocytes for ovarian cancer therapy. Hum Gene Ther 29: 614-625, 2018. PMID: 29343771. DOI: 10.1089/hum.2017.080

110 Jones BS, Lamb LS, Goldman F and Di Stasi A: Improving the safety of cell therapy products by suicide gene transfer. Front Pharmacol 5: 254, 2014. PMID: 25505885. DOI: 10.3389/fphar.2014.00254

111 Cogdill AP, Andrews MC and Wargo JA: Hallmarks of response to immune checkpoint blockade. Br J Cancer 117: 1-7, 2017. PMID: 28524159. DOI: 10.1038/bjc.2017.136

112 Liu X, Ranganathan R, Jiang S, Fang C, Sun J, Kim S, Newick K, Lo A, June CH, Zhao Y and Moon EK: A chimeric switch-receptor targeting PD1 augments the efficacy of second-generation CAR T cells in advanced solid tumors. Cancer Res 76: 1578-1590, 2016. PMID: 26979791. DOI: 10.1158/0008-5472.CAN-15-2524

113 John LB, Devaud C, Duong CPM, Yong CS, Beavis PA, Haynes NM, Chow MT, Smyth MJ, Kershaw MH and Darcy PK: Anti-PD1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. Clin Cancer Res 19: 5636-5646, 2013. PMID: 23873688. DOI: 10.1158/1078-0432.CCR-13-0458

114 Gargett T, Yu W, Dotti G, Yvon ES, Christo SN, Hayball JD, Lewis ID, Brenner MK and Brown MP: GD2-specific CAR T cells undergo potent activation and deletion following antigen encounter but can be protected from activation-induced cell death by PD-1 blockade. Mol Ther 24: 1135-1149, 2016. PMID: 27019998. DOI: 10.1038/mt.2016.63

115 Hill BT, Roberts ZJ, Xue A, Rossi JM and Smith MR: Rapid tumor regression from PD-1 inhibition after anti-CD19 chimeric antigen receptor T-cell therapy in refractory diffuse large B-cell lymphoma. Bone Marrow Transplant 55: 1184-1187, 2020. DOI: 10.1038/s41409-019-0657-3

116 Kim D-S, Dastidar H, Zhang C, Zemp FJ, Lau K, Ernst M, Rakic A, Sikdar S, Rajwani J, Naumenko V, Balce DR, Ewanchuk BW, Tailor P, Yates RM, Jenne C, Gafiuk C and Mahoney DJ: Smac mimetics and oncolytic viruses synergize in driving anticancer T-cell responses through complementary mechanisms. Nat Commun 8: 344, 2017. PMID: 28839138. DOI: 10.1038/s41467-017-00324-x

117 Scott EM, Duffy MR, Freedman JD, Fisher KD and Seymour LW: Solid tumor immunotherapy with T cell engager-armed oncolytic viruses. Macromol Biosci 18, 2018. PMID: 28902983. DOI: 10.1002/mabi.201700187

118 Ajina A and Maher J: Prospects for combined use of oncolytic viruses and CAR T-cells. J Immunother Cancer 5: 90, 2017. PMID: 29157300. DOI: 10.1186/s40425-017-0294-6

119 Bracci L, Schiavoni G, Sistigui A and Belardelli F: Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ 21: 15-25, 2014. PMID: 23787994. DOI: 10.1038/cdd.2013.67

120 Vierboom MP, Bos GM, Ooms M, Offeringa R and Melief CJ: Cytospermaphide enhances anti-tumor effect of wild-type p53-specific CTLs. Int J Cancer 87: 253-260, 2000. PMID: 10861484. DOI: 10.1002/1097-0215(20000715)87:2<253::aid-ijc17>3.0.co;2-a

121 Ramakrishnan R, Huang C, Cho HJ, Lloyd M, Johnson J, Ren X, Altiok S, Sullivan D, Weber J, Celis E and Gabrilovich DI: Autophagy induced by conventional chemotherapy mediates tumor cell sensitivity to immunotherapy. Cancer Res 72: 5483-5493, 2012. PMID: 22942258. DOI: 10.1186/1475-2861-12-2236

122 Parente-Pereira AC, Whilling LM, Brewig N, van der Stegen SJ, Davies DM, Wilkie S, van Schalkwijk MCI, Ghaem-Maghami S and Maher J: Synergistic chemoimmunotherapy of epithelial ovarian cancer using ErbB-retargeted T cells combined with carboplatin. J Immunol 191: 2437-2445, 2013. PMID: 23898037. DOI: 10.4049/jimmunol.1301119

123 Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymeric L, Yang H, Portela Catani JP, Hannami D, Duret H, Steegh K, Martins I, Schlemmer F, Michaud M, Kepp O, Sukkurwala AQ, Menger L, Vaccelli E, Droin N, Galluzzi L, Krzysiek R, Gordon S, Taylor PR, Van Endert P, Solary E, Smyth MJ, Zitvogel L and Kroemer G: Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity 38: 729-741, 2013. PMID: 23562161. DOI: 10.1016/j.immuni.2013.03.003

124 Lutsiaj ME, Semnani RT, De Pascalis R, Kashmiri SVS, Schlom J and Sabzevari H: Inhibition of CD4(+)CD25(+) T regulatory cell function implicated in enhanced immune response by low-dose cyclophosphamide. Blood 105: 2862-2868, 2005. PMID: 15591121. DOI: 10.1182/blood-2004-06-2410

125 Xu J, Wang Y, Shi J, Liu J, Li Q and Chen L: Combination therapy: A feasibility strategy for CAR-T cell therapy in the treatment of solid tumors. OncoLett 16: 2063-2070, 2018. PMID: 30008901. DOI: 10.3892/ol.2018.8946

126 Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Mairuci MC, Ulrich E, Saulnier P, Yang H, Amigorena S, Ryffel B, Barrat FJ, Safigt P, Levi F, Lidereau R, Nogues C, Mira J-P, Chompret A, Joulin V, Clavel-Chapelon F, Maghami S and Maher J: Synergistic chemoimmunotherapy of epithelial ovarian cancer using ErbB-retargeted T cells combined with carboplatin. J Immunol 191: 2437-2445, 2013. PMID: 23898037. DOI: 10.4049/jimmunol.1301119

127 Higgins JP, Bernstein MB and Hodge JW: Enhancing immune responses to tumor-associated antigens. Cancer Biol Ther 8: 1440-1449, 2009. PMID: 19556848. DOI: 10.4161/cbt.8.15.9133
Schlom J, van Veelen P and Neefjes JJ: Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med 203: 1259-1271, 2006. PMID: 16636135. DOI: 10.1084/jem.20052494

129 Lugade AA, Sorensen EW, Gerber SA, Moran JP, Frelinger JG and Lord EM: Radiation-induced IFN-gamma production within the tumor microenvironment influences antitumor immunity. J Immunol Baltim Md 1950 180: 3132-3139, 2008. PMID: 18292536. DOI: 10.4049/jimmunol.180.5.3132

130 Liao Y-P, Wang C-C, Butterfield LH, Economou JS, Ribas A, Meng WS, Iwamoto KS and McBride WH: Ionizing radiation affects human MART-1 melanoma antigen processing and presentation by dendritic cells. J Immunol 173: 2462-2469, 2004. PMID: 15294960. DOI: 10.4049/jimmunol.173.4.2462

131 Buka D, Dvořák J, Sitorová V, Hátlová J, Richter I and Sirák I: Changes in the CD8+ density of tumor infiltrating lymphocytes after neoadjuvant radiochemotherapy in patients with rectal adenocarcinom. Klin Onkol 29: 204-209, 2016. PMID: 27296405. DOI: 10.14735/amko2016204

132 Aranda F, Buqué A, Bloy N, Castoldi F, Eggermont A, Cremer I, Fridman WH, Fucikova J, Galon J, Spisek R, Tartour E, Zitvogel L, Kroemer G and Galluzzi L: Trial Watch: Adoptive cell transfer for oncological indications. Oncoimmunology 4: e1046673, 2015. PMID: 26451319. DOI: 10.1080/2162402X.2015.1046673

133 Zitvogel L, Kepp O and Kroemer G: Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 8: 151-160, 2011. PMID: 21364688. DOI: 10.1038/nrclinonc.2010.223

134 Perica K, Varela JC, Oelke M and Schneck J: Adoptive T cell immunotherapy for cancer. Rambam Maimonides Med J 6, 2015. PMID: 25717386. DOI: 10.5041/RMMJ.10179

Received January 7, 2021
Revised January 20, 2021
Accepted January 22, 2021