

Genetically engineered T cell and tumour-infiltrating lymphocyte therapies

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Summary

Haemato-oncology has made significant progress in recent years, particularly through the development of innovative immunotherapeutic approaches such as CAR T cell (chimeric antigen receptor T cell) and tumour-infiltrating lymphocyte therapies. Both methods use the patient's own immune system to treat cancer, but in different ways. CAR T cell therapy is a form of immunotherapy in which the patient's own T cells are genetically modified. CAR T cell therapies have proven to be particularly effective in haematological B-cell neoplasms, such as B-cell acute lymphoblastic leukaemia (B-ALL) and B-cell lymphomas, as well as in multiple myeloma. Tumour-infiltrating lymphocyte therapy, on the other hand, exploits the natural ability of T cells to recognise tumour-associated antigens of tumour cells with the T cell receptor. Tumour tissue is taken from the patient then tumour-infiltrating lymphocytes are isolated from it. These tumour-infiltrating lymphocytes are expanded *ex vivo* to increase their number and activity. This review discusses the principles of these innovative therapies. Both therapies represent significant advances in personalised cancer treatment and offer new hope for our cancer patients.

Introduction

Cancer immunotherapy has significantly improved the outcome of patients. In particular, the introduction of immune checkpoint inhibitors has transformed the treatment of patients with solid cancers [1, 2]. However, only a limited number of patients benefit from immune checkpoint inhibition [3]. Cell therapies including genetically engineered T cells expressing a chimeric antigen receptor (CAR) have been used to treat cancer patients [4]. While such CAR T cell therapies have been successfully used mainly to treat

patients with haematological B cell neoplasia, naturally occurring tumour-infiltrating lymphocytes (TILs) have been used for the treatment of solid cancers resistant to immune checkpoint inhibitors [5]. Here, we give an overview of these two emerging cell therapy approaches (figure 1) and an outlook on current developments.

CAR T cell therapy

Cellular cancer therapies have been used to treat cancer since the introduction of allogeneic stem cell transplantation by Don Thomas in the 1970s [6]. In the late 1980s, T cells were genetically modified for the first time, equipping them with a synthetic T cell receptor containing an intracellular activation domain, the CD3 ζ of the T cell receptor, and an extracellular binding domain, usually a single-chain variable fragment (scFv) of an antibody directed against a surface molecule on the cancer cell [7] (figure 2). These so-called chimeric antigen receptors (CARs) were further developed, showing a good effect in mouse models but also in patients with B-cell neoplasia [4]. Further development led to the so-called second-generation CARs, which also contained a co-stimulatory component in the intracellular domain [4]. The intracellular domain of CD28 or 4-1BB (CD137) was primarily used for this purpose (figure 2). This enabled not only recognition of the target antigen but also proliferation and persistence of these cells *in vivo*. More recent developments include other co-stimulatory domains or synthetic proteins that lead to an increase in specificity or efficiency as well as the possibility of better control of their proliferation. In contrast to antibodies targeting a tumour surface antigen such as the anti-CD20 antibody rituximab, CAR T cells can persist and lead to long-term control by the immune system.

Haematological diseases

The treatment of B cell malignancies with cellular immunotherapies has become the standard of care for several indications [4, 8]. Treatment is currently approved when initial treatment has failed or in refractory cases (table 1). In particular, CD19-positive B cell malignancies have been successfully treated with CD19-specific CAR T cells [4, 8]. CAR T cell therapy was able to achieve durable remissions in patients after multiple prior lines of therapy and

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ABBREVIATIONS

B-ALL:	acute B-cell lymphoblastic leukaemia
CAR:	chimeric antigen receptor
DLBCL:	diffuse large B-cell lymphoma
scFv:	single-chain variable fragment
TIL:	tumour-infiltrating lymphocyte

Figure 1: Illustration of tumour-infiltrating lymphocyte (TIL) therapy (left) and CAR T cell therapy. In tumour-infiltrating lymphocyte therapy, T cells are isolated from the tumour and expanded to $>50 \times 10^9$ cells with IL-2, CD3 stimulation and allogeneic feeders. After lymphodepletion with cyclophosphamide and fludarabine, the CD3-positive T cells are administered to the patient together with IL-2. CAR T cell therapy uses T cells obtained by apheresis. The T cells are then genetically manipulated (usually with a lenti- or retroviral vector) so that they stably express a CAR. They are then returned to the patient who has undergone lymphodepletion.

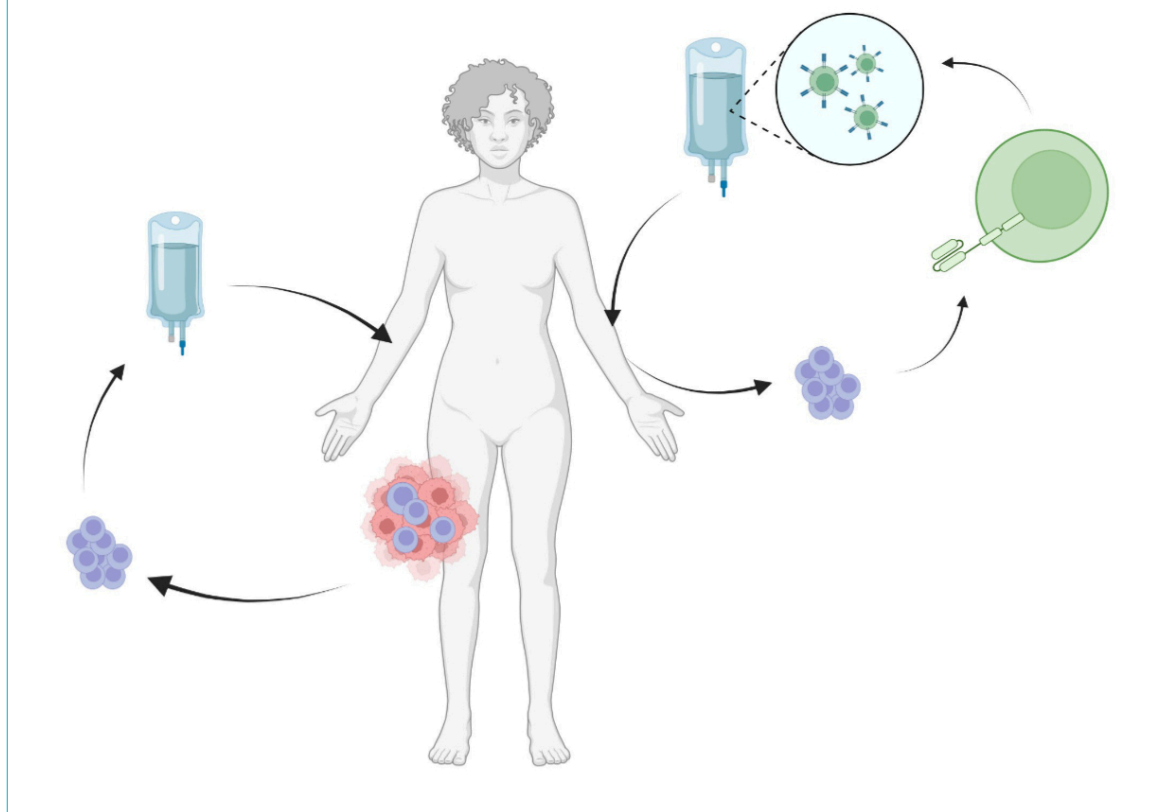
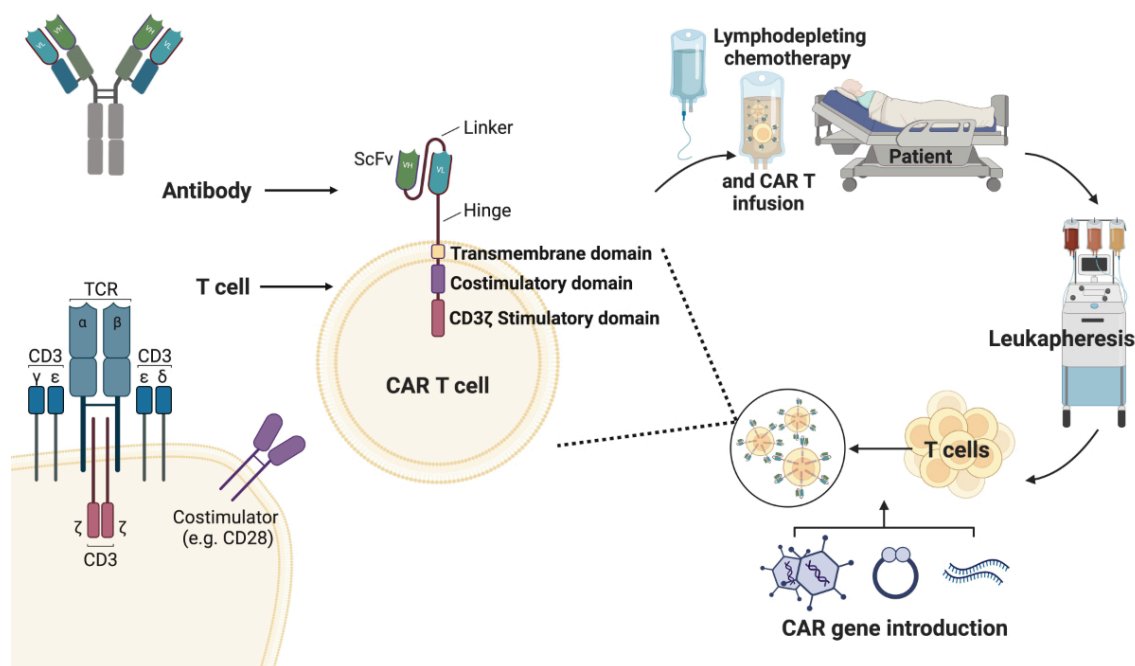


Figure 2: Demonstration of the genetic modification of T cells during CAR T cell production. Chimeric antigen receptors (CARs) are synthetic proteins consisting of an intracellular part with different signalling domains and an antigen-binding domain that is commonly derived from an antibody and expressed as a short-chain variable fragment (ScFv). CAR constructs are delivered to T cells after a leukapheresis and retransfused in the lymphodepleted patient. TCR: T cell receptor. Created with BioRender.com.



in some cases highly chemotherapy-refractory disease. Recently, several studies have also shown an advantage of CAR T cell therapy in patients with relapsed/refractory diffuse large B-cell lymphoma compared to the standard of care with chemotherapy followed by autologous stem cell transplantation (diffuse large B-cell lymphoma) [4, 8]. For example, in the ZUMA-7 study, axicabtagene-ciloleucel (Axi-cel) was tested in 359 patients compared to standard treatment [9]. In addition to the CD19-targeted CAR T cell therapies, CAR T cells against the BCMA antigen have also been established for the treatment of multiple myeloma [10, 11]. Other targets on myeloma cells such as SLAMF-7 or G protein-coupled receptor, class C, group 5, member D (GPC5D) are currently being investigated [12].

Solid cancers

Several targets for solid tumours are currently under investigation. Early trials for HER2-positive cancers were terminated due to severe toxicity on target tissues outside the tumour (so-called on-target/off-tumour effects) [4, 8]. Major hurdles for CAR T cell therapy in solid malignancies include defining the correct tumour antigen with specific, high-level expression in the tumour, difficulties in trafficking T cells into the tumour microenvironment and depletion of CAR T cells due to an immunosuppressive tumour microenvironment [4, 8]. Nevertheless, some successful studies have already been conducted. For example, a promising response to claudin 18.2-targeted CAR T cells has been shown in patients with advanced gastric or pancreatic cancer [13]. An interesting approach was pursued by Mackensen and colleagues. In addition to the use of claudin 6-directed CAR T cells, a combination with an RNA vaccine, which induces additional activation of the CAR T cells with enhancement of a memory function, was pursued. The study showed promising results in gastrointestinal and gynaecological malignancies [14]. In recent months, several studies on the treatment of glioblastoma with CAR T cells have also been published [15, 16]. One by Bagley et al. used intrathecally administered CAR T cells able to recognise two antigens on glioblastoma cells, namely EGFR and IL13Ralpha2 [16]. The other by Marcela Maus' group used locally administered CAR T

cells that recognise both the tumour-specific variant of EGFRvIII and the wild-type variant of EGFR. Promising results were also achieved with anti-GD2 CAR T cells in paediatric gliomas, with complete remissions being induced [17]. So far, however, the long-term results are very sobering; they show that the principle also works in solid tumours but that further work is needed to achieve longer-term tumour control or eradication. Recently, the first genetically engineered cell product for solid tumours has been approved by the FDA; however it is not a CAR T cell therapy but a T cell receptor T cell therapy targeting the tumour antigen MAGE-A4. Afamitresgene autoleucel was successfully tested in HLA-A*02:01-, 02-, 03- and 06-positive patients with metastatic synovial sarcoma [18].

Various additional measures can potentially increase the efficiency of CAR T cells against solid tumours. For example, to increase the specificity of the CAR construct, genetic systems have been developed that can integrate two or more tumour-transmitted signals [4, 8]. The synNOTCH system, for example, uses the Notch signalling system to mediate a two-step activation of CAR T cells [19]. The binding of a first antigen induces the expression of the activating CAR, which leads to the activation of the immune cell. This two-step CAR T cell activation can significantly increase the specificity of such a CAR T cell product. The local release of cytokines that promote anti-tumour immunity could improve the activation and efficacy of CAR T cells [8]. For example, secretion of IL-12 could enhance CD19-targeted CAR T cell therapy [20].

CAR T cell therapy for patients with autoimmune disease

Recently, several reports have been published describing a role for CAR T cell therapy in patients with autoimmune disease [21–27]. For example, patients with treatment-refractory systemic lupus erythematosus (SLE) treated with CD19-directed CAR T cells experienced significant improvement [21–24]. Also, CD19-targeted CAR T cell therapies were used to treat patients with treatment-refractory anti-synthetase syndrome [25, 26, 28] or patients with multiple sclerosis and myasthenia gravis [27, 29].

Table 1:
EMA-approved CAR T therapies for B cell malignancies and multiple myeloma (as of September 2024).

Product	Kymriah	Yescarta	Tecartus	Breyanzi	Abecma	Carvykti
Active substance	Tisagenlecleucel	Axicabtagene-ciloleucel	Brexucabtagene autoleucel	Lisocabtagene maraleucel	Idecabtagene-vicleucel	Ciltacabtagenium autoleucel
Manufacturer	Novartis	Kyte/Gilead	Kyte/Gilead	BMS/Celgene	BMS/Celgene	Janssen
Approval (EMA)	2018	2018	2020	2022	2021	2022
Target	CD19	CD19	CD19	CD19	BCMA	BCMA
Costimulatory signal	4-1BB	CD28	CD28	4-1BB	4-1BB	4-1BB
Indication(s)	r/r B-ALL (age ≤25, 3 rd line); r/r DLBC (3 rd line); r/r FL (3 rd line)	r/r DLBCL, HGBCL (2 nd line*); PMBCL (3 rd line); r/r FL (4 th line)	r/r MCL (3 rd line; previous lines included BTK inhibitor); r/r B-ALL (age ≥26, 3 rd line)	r/r DLBCL, PMBCL, HGBCL (2 nd line*); FL grade 3B (2 nd line*)	r/r MM (3 rd line**)	r/r MM (2 nd line***)

B-ALL: acute B-cell lymphoblastic leukaemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high-grade B-cell lymphoma; MCL: mantle cell lymphoma; MM: multiple myeloma; PMBCL: primary mediastinal B-cell lymphoma; r/r: relapsed/refractory.

* 2nd line if refractory or early relapse (within 12 months after first-line chemoimmunotherapy); 3rd line if later.

** After at least 2 lines including an immunomodulator, proteasome inhibitor and anti-CD38 antibody.

*** After 1 line including an immunomodulator, proteasome inhibitor and refractory to lenalidomide.

Side effects of CAR T cell therapy

CAR T cell therapy is considered a promising cancer treatment but is associated with various side effects, some of which can be life-threatening [30]. One of the most common side effects is cytokine release syndrome (CRS), which can cause fever, low blood pressure and organ dysfunction. In addition, immune effector cell-associated neurotoxicity syndrome (ICANS) can occur, a reversible but potentially life-threatening complication that can manifest with confusion, seizures and other neurological symptoms [31]. In phase III trials of second-line therapy for patients with diffuse large B-cell lymphoma, second-generation CAR T cells showed that up to 90% of patients experienced cytokine release syndrome and 60% neurological side effects [32]. However, most of these side effects were not severe and were manageable. Mild cytokine release syndrome is treated with supportive measures such as antipyretics and hydration. More severe cytokine release syndrome requires the use of IL-6R blocking antibodies and immunosuppressants such as corticosteroids [33]. In severe cases, patients may need to be transferred to the ICU for circulatory monitoring and possibly oxygen or respiratory support. While IL-6 blockade is often effective in cytokine release syndrome, it does not help in immune effector cell-associated neurotoxicity syndrome and may even worsen the clinical picture. In addition to supportive measures, corticosteroids are used here, possibly in combination with anakinra. Improvements in CAR design could potentially reduce these sometimes life-threatening side effects. It is known that CARs with a CD28 co-stimulatory domain (e.g. axi-cel) proliferate faster and release higher cytokine concentrations, which can lead to earlier and more-severe cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome compared to 4-1BB-containing CARs (e.g. tisa-cel) [31]. Initial studies suggest that changes in the signalling domain of the CD3 ζ chain may improve the side effect profile. Medium-term complications include cytopenias, infections and disease relapse. In the latter case, the therapeutic options are very limited and the prognosis is very poor. An increased risk of secondary malignancies has been reported but further studies, in particular to better understand the association, are warranted. Further challenges are the numerous resources and logistics that such a therapy requires. As a result, the costs are also very high.

Tumour-infiltrating lymphocytes

The use of cellular therapy with tumour-infiltrating lymphocytes has been practiced for several decades, but only in specialised clinics [34–36]. The first patients were treated in the late 1980s [35]. In tumour-infiltrating lymphocyte therapy, T cells are isolated from a sample of the primary tumour or a metastasis [37]. By using IL-2, T cells are activated and multiplied. The treatment works in some patients because tumour-specific T cell clones are present in the resected lesion. These tumour-specific T cells have a T cell receptor that recognises an antigen expressed by the tumour. After lymphodepletion with cyclophosphamide and fludarabine, the tumour-infiltrating lymphocyte product is administered together with IL-2 [37]. Recently, a randomised phase III study conducted in the Netherlands and Denmark in patients with metastatic melanoma was pub-

lished [5]. Here it was shown that after failure of a standard immunotherapy with immune checkpoint inhibition against PD-1, patients responded better to tumour-infiltrating lymphocyte therapy than to a second-line immune checkpoint inhibition with antibodies directed against CTLA-4. In addition, a commercial product, lifileucel, was recently approved by the FDA in the USA for the treatment of melanoma patients. We have recently conducted the BaseTIL study, in which we treated 9 patients with advanced and heavily pre-treated melanoma [38]. In addition to melanoma patients, in principle all patients with T cells containing T cell receptors that recognise a tumour antigen (often so-called neoantigens, which arise through new mutations in cancer cells) can be treated. Patients with non-small cell lung cancer (NSCLC) have also been successfully treated with tumour-infiltrating lymphocytes [39]. Other immunogenic tumour entities such as cervical carcinoma can also potentially be treated with tumour-infiltrating lymphocyte therapy. We have recently opened a trial for patients with NSCLC at the University Hospital in Basel (NCT06455917).

Tumour-infiltrating lymphocyte therapies can of course also be improved. For example, the T cells that recognise tumour antigens can be separated from the other T cells in the tumour. Thus, potentially much larger numbers of T cells attacking the tumour can be isolated and amplified [37, 40]. In order to obtain a more functional phenotype of the T cells, other cytokines or stimulating antibodies can also be added for *in vitro* expansion [40]. Tumour-infiltrating lymphocyte therapy can also be combined with other substances. For example, tumour-infiltrating lymphocyte therapy has already been combined with immune checkpoint inhibitors in various studies. In some cases, a good response to this combination therapy was observed in patients with NSCLC [41]. Other forms of IL-2 can also be used. There are newer IL-2 preparations that can specifically stimulate the cytotoxic T cells rather than the regulatory T cells [42]. We are currently conducting the BaseTIL-03M study in Basel, which is testing a combination of such a new IL-2 preparation together with tumour-infiltrating lymphocyte therapy in melanoma patients (NCT05869539).

Side effects of tumour-infiltrating lymphocyte therapy

Cytopenias following lymphodepleting chemotherapy and thus infections and bleeding complications are the most common side effects of tumour-infiltrating lymphocyte therapy [5]. Interleukin-2 therapy can also cause cytokine release syndrome, depending on the dose and intensity of IL-2 administration. In addition to cytokine release syndrome, IL-2 treatment can also lead to vascular leak syndrome, sometimes with pulmonary oedema [37]. It is therefore important to consider the use of vasoactive substances at an early stage. As tumour-infiltrating lymphocyte therapy is a classic immunotherapy, immune-mediated side effects with various organ toxicities can also occur, as with immune checkpoint inhibitor therapy [40]. These often have to be treated with steroids, depending on which organs are involved.

Outlook

Emerging cellular therapies, such as CAR T cell therapy and tumour-infiltrating lymphocyte therapy, have significantly improved prognosis for certain patients. CAR T cell therapies are now routinely used for haematological cancers, primarily B-cell lymphomas, and efforts are underway to expand CAR T cell treatments to additional tumour types. Moreover, CAR T cell therapies may soon offer new treatment options for selected patients with refractory autoimmune diseases and a multitude of studies are ongoing [14]. Tumour-infiltrating lymphocyte therapy also holds promise for inducing long-term remissions in patients with immunogenic tumours. With the recent approval of a commercial tumour-infiltrating lymphocyte product for treating melanoma in the United States, this treatment has become accessible to a wider patient population. Trials are currently evaluating its effectiveness for other tumour types, and advancements in expanding tumour-specific T cells are expected to enhance its efficacy.

The availability of these cellular therapies will place new demands on treatment centres, as more patients are expected to seek these specialised options. While the costs of these therapies, including associated treatments and potential complications, remain high, future logistical improvements may help manage expenses. For example, some centres are already producing tumour-infiltrating lymphocyte therapies in their own cleanroom facilities, which may reduce production costs over time. Additionally, certain preparatory and therapeutic steps may transition to outpatient settings, making these therapies more accessible.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *HL* has a grant from Fond'Action for TIL therapy and drug support for a TIL trial from Anaveon. *AH* received support for attending meetings and/or travel from Amgen (EHA Congress 2025) and Kite/Gilead (EHA-EBMT 7th European CAR T-cell Meeting) and has stock or stock options from Novartis.

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