Defeating Cancer with Armed Antibodies and Genetically Modified Immune Cells

Lutong Zhao *

Trinity College Dublin, Dublin, Ireland

* Corresponding Author Email: zhaolutong0628@gmail.com

Abstract. Cancer has been one of the primary causes of lethality worldwide, driving the demand for innovative treatments alongside traditional methods like surgery, chemotherapy and radiotherapy. Advances in immunotherapy, particularly with antibody-drug conjugators (ADCs) and genetically modified immune cells, such as CAR-T and TCR-T cells, are bringing the goal of defeating cancer closer to reality. ADCs enable the precise delivery of cytotoxic drugs to cancer cells while sparing healthy tissue; CAR-T and TCR-T cells are genetically engineered to enhance immune targeting against tumours. However, these therapies still need to overcome challenges, including side effects, production complexity, and high costs. A synergistic approach that combines ADCs with modified immune cells can solve the problem of tumour heterogeneity and drug resistance. This dual-targeting strategy amplifies cancer cell lethality by combining ADC-induced cytotoxicity with a sustained immune response from CAR-T and TCR-T cells. In addition, early clinical trials have demonstrated that this combination therapy, especially in drug-resistant cancers, improves patient survival and reduces recurrence rates. Although synergetic therapy is still facing problems regarding immune-related side effects and accessibility, this integration effectively enhances cancer immunotherapy, which is personalised, long-lasting, and effective.

Keywords: Antibody-Drug Conjugates (ADCs); CAR-T and TCR-T cell therapy; Cancer immunotherapy; Synergistic cancer treatment; Tumor heterogeneity and drug resistance.

1. Introduction

Cancer has been considered a significant cause of mortality worldwide, especially in an ageing population, as rising life expectancy has driven an increase in cancer incidence. When normal cells accumulate many irreparable genetic mutations, the proliferation of these cells will become uncontrolled and eventually form tumours, a process known as tumorigenesis. In order to fight cancer, there are three more mature traditional treatment methods at this stage, namely surgery, chemotherapy, and radiation therapy [1]. Specifically, surgery physically removes tumours, chemotherapy applies drugs to inhibit cancer cell growth, and radiation uses targeted radiation to destroy cancer cells. However, these traditional therapies have limitations including unavoidable side effects, incompleted targeting and relatively high recurring possibility of cancer [2].

In recent years, immunotherapy has been added as the fourth method of traditional cancer therapy. Opposite to the previous three therapies that treat patients externally, immunotherapy uses the body's own immune system to recognise and attack tumour cells. This is a way to improve the targeting specificity and immune memory of a patient's immune system. Moreover, due to the high research and development cost of targeted therapeutic drugs to meet the conditions of "precision medicine", in this context, innovative therapies with research and development advantages such as antibody-drug coupling (ADC) or "armed antibodies" have attracted attention [1]. In detail, when a patient uses antibody-coupled drugs, the antibodies circulate into the body. These antibodies then recognise the cancer cells and attach to them, thus launching a direct attack on the cancer cells. Then, when they start working, the antibodies attack the cancer cells directly. Therefore, the ADC has extremely high targeting accuracy. In addition to ADCs, genetically modified immune cells, such as the high-profile chimeric antigen receptor T-cell (CAR-T) and T-cell receptor engineered T Cells (TCR-T), promising new areas for cancer treatment have been introduced [1, 2].

ADCs and genetically engineered immune cells provide personalised therapies to patients with unique cancerous characteristics by various combinations of the two methods. This is a synergetic

strategy that not only overcomes tumour heterogeneity, but also allows highly precise targeting of tumour cells while reducing the potential drug resistance [3]. Although these innovative therapies have been demonstrated and made progress through a large number of clinical trials over the years, there are problems that still need to be overcome. For example, CAR-T and TCR-T therapies have a high risk of side effects, including cytokine release syndrome (CRS) and immune-related neurotoxicity [4]. Furthermore, these therapeutic products hae high complexity and costs during the manufacturing that limit their wider applications. Despite these limitations, combinations of armed antibodies and genetically engineered immune cells are a milestone in cancer immunotherapy that provides highly effective and personalised cancer treatment. This review focuses on the mechanisms, applications and limitations of ADC, CAR-T, and TCR-T therapies, as well as their potential in synergistic cancer treatment.

2. Design and Application of Armed Antibodies

2.1. Concept and Mechanism of Armed Antibodies

Armed antibodies, scientifically referred to as Antibody-Drug Conjugates (ADCs), are a novel class of biopharmaceutical agents designed to combine the specificity of monoclonal antibodies (mAbs) with the potent cytotoxic effects of chemotherapy drugs. Each type of ADC is composed of three key components, which are one monoclonal antibody and one cytotoxic payload connected by a chemical linker region. Specifically, the antigen that the monoclonal antibody binds to is primarily expressed on tumour cells, reducing the potential off-target effects. It is released only under specific conditions within the tumour microenvironment, such as low pH or enzymatic activity. Depending on its design, the linker can be cleavable or non-cleavable, deciding how and when the drug will be released [5]. Once the drugs are released inside the target cells, they will effectively induce cell death through DNA damage or disrupting microtubule functions.

As mentioned above, the mechanism of ADCs begins with the binding of monoclonal antibodies to their specific antigen on tumour cells, which triggers the internalisation of ADCs via the cellular process named endocytosis. The ADC molecules are firstly enclosed by cell membranes that form a bubble-like endosome. Under an acidic environment within the endosome, the linker region of ADC is cleaved to allow the drug to be released into the intracellular space where it functions. Some of the ADCs perform a "bystander effect" in that their released drugs are able to diffuse into adjacent cells for a broadened therapeutic effect. In addition to intracellular effects, ADCs can further induce an immune response by activating complement- and antibody-dependent cytotoxicity, which enhances the anti-cancer efficacy of ADCs [3].

2.2. Common Armed Antibody Drugs

Antibody-drug conjugates (ADCs) using monoclonal antibodies directly deliver the cytotoxic drugs into tumour cells. Among the most significant ADCs are Brentuximab Vedotin, Trastuzumab Emtansine (T-DM1), Trastuzumab Deruxtecan (T-DXd), and Sacituzumab Govitecan, each of which targets distinct cancer-related antigens and utilises different cytotoxic payloads.

Brentuximab vedotin (Adcetris) targets CD30, a receptor commonly found in Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL) [6]. By binding to CD30 on malignant cells, Brentuximab vedotin is internalized into the tumour cell, and its cytotoxic payload, Monomethyl Auristatin E (MMAE), is released. MMAE disrupts tubulin polymerisation, halting cell division and leading to apoptosis [7]. This ADC has effectively treated relapsed or refractory Hodgkin lymphoma and systemic ALCL by precisely targeting CD30-positive cancer cells while reducing the risk of systemic toxicity [8].

Trastuzumab Emtansine (T-DM1 or Kadcyla) is another ADC that targets HER2, a receptor overexpressed in certain breast cancers [6]. T-DM1 combines the HER2-targeting ability of Trastuzumab with the cytotoxic agent DM1, a microtubule inhibitor. Once internalised by HER2-positive cells, DM1 is released, disrupting microtubule activities and leading to cell death. T-DM1

has proven especially useful in HER2-positive breast cancer patients resistant to prior HER2-targeting therapies [7]. Using a non-cleavable linker, T-DM1 ensures that the cytotoxic agent is only released inside cancer cells, reducing systemic side effects [6].

Similarly, Trastuzumab Deruxtecan (T-DXd or Enhertu) targets HER2 but offers enhanced therapeutic effects through a topoisomerase I inhibitor payload, Deruxtecan [7]. This payload prevents DNA replication and induces cell death. T-DXd is particularly notable for its bystander effect, allowing the cytotoxic agent to impact neighbouring antigen-negative cells, making it a powerful option for treating cancers with heterogeneous HER2 expression [6]. Its use has expanded beyond HER2-positive breast cancer to include HER2-mutated non-small cell lung cancer and gastric cancer [8]. This versatility and its ability to overcome resistance to previous HER2-targeted therapies make T-DXd a highly promising ADC [7].

Sacituzumab Govitecan (Trodelvy) takes a different approach, targeting TROP-2, a protein overexpressed in several epithelial cancers, including triple-negative breast cancer (TNBC) [7]. The ADC is conjugated to SN-38, an active metabolite of the chemotherapy drug irinotecan, which inhibits topoisomerase I, leading to DNA damage and apoptosis [8]. Sacituzumab Govitecan has shown significant promise in treating aggressive cancers such as TNBC, where treatment options are limited [7]. Its precise targeting of TROP-2 and the powerful cytotoxic effect of SN-38 have made it a critical tool in managing these difficult-to-treat cancers [8].

2.3. Advantages of Armed Antibodies

Antibody-drug conjugates (ADCs) take advantage of combining the specificity of their monoclonal antibody and the cytotoxicity of the drug. ADCs also allow selective targeting directly to the tumour cells, which optimises the least damage to the healthy tissue surrounding the tumour [9]. This precision is achieved by the recognition of tumour-related antigens, and it addresses the targeting selectivity that is lacking in some traditional therapies[7, 10].

One key benefit of ADCs is their ability to reduce systemic side effects. Unlike traditional chemotherapy, which can harm healthy tissues, ADCs release their cytotoxic payloads only after binding to specific target antigens, focusing their effects on cancer cells. This targeted release allows higher doses of cytotoxic agents to be administered safely [6, 10]. Additionally, ADCs can further increase their cytotoxity through the "bystander effect" that is important in treating tumours with heterogeneous antigen. In other words, the released drug affects not only the antigen-positive cells but also the nearby antigen-negative cells [7]. For example, the payload of Trastuzumab Deruxtecan, an ADC, can diffuse from the target cell to neighboring cells that may have low or heterogeneous HER2 expression [9].

2.4. Challenges and Side Effects

Despite their advantages, the clinical use of ADCs is hindered by several challenges, particularly drug resistance, linker stability, and immune-related adverse effects. First, drug resistance has arisen since tumour cells can become more adaptive to ADCs. This adaption is achieved by changing the internalisation pathway of the ADC-antigen complex and when the targeted antigen is down-regulated, lost, or mutated [7, 8]. Additionally, linker stability is another crucial factor for ADC effectiveness. The chemical linkers connecting the cytotoxic payload to the antibody must be stable in the bloodstream to prevent premature drug release but must also efficiently cleave inside target cells. An unstable linker can lead to off-target effects, while an overly stable linker may prevent proper drug release at the tumour site, reducing therapeutic impact [6].

Moreover, immune-related reactions pose additional challenges. Although ADCs are designed to specifically target cancer cells, they can inadvertently provoke immune-mediated toxicities. This transpires when immune mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) inadvertently damage normal tissues that exhibit low amounts of the target antigen. Furthermore, hypersensitivity reactions or immune responses to the

cytotoxic payload can complicate patient management and decrease the overall tolerability of treatment [8].

3. Types and Applications of Genetically Modified Immune Cells

3.1. CAR-T Cell Therapy

Chimeric antigen receptor T (CAR-T) cell therapy is a standard immunotherapy that utilises genetically engineered T cells to target and eliminate tumour cells. This approach is achieved by modifying the T cells to express chimeric antigen receptors (CARs) which is able to recognise specific tumour antigens. The components of a CAR molecule include an extracellular antigen-binding domain derived from a single-chain variable fragment (scFv) of an antibody, a hinge region for flexibility, a transmembrane domain, and an intracellular signalling domain [2].

The development of CAR-T cell therapy has greatly benefited from gene-editing technologies like CRISPR/Cas9. By precisely modifying the genetic composition of T-cells, CRISPR is able to increase anti-cancer ability while reducing adverse impacts. For example, CRISPR has been applied to remove checkpoint molecules such as PD-1 that inhibit T-cell activity. After removing this inhibition, the produced CAR-T cells are more long-lasting and less prone to exhaustion. The combination of CRISPR and CAR T-cells holds promise for creating more effective and personalised treatments for cancer patients [11].

CAR-T cell therapy primarily targets specific antigens present in cancer cells. For instance, the most commonly targeted antigen in CAR-T therapy is CD19, which is expressed in B-cell malignancies such as acute lymphoblastic leukaemia (ALL) and certain types of non-Hodgkin lymphoma (NHL) [12]. When CAR-T cells encounter a cancer cell expressing CD19, the scFv domain of the CAR binds to the CD19 antigen in a highly specific manner. Upon this antigen recognition, the binding signal is transmitted from the extracellular scFv through the transmembrane domain to the intracellular signalling domains of the CAR. These signalling domains, including CD3ζ and co-stimulatory molecules such as CD28 or 4-1BB, trigger CAR-T cells to proliferate, produce cytokines, and exert cytotoxic immune response, leading to apoptosis in the target B cells [12]. Additionally, the CAR-T cells amplify the attack on the cancer cells by recruiting other immune cells, effectively eliminating CD19-positive B cells, whichever are healthy or malignant [2, 12].

The success of CD19-targeted CAR-T cell therapy has been evident in clinical trials such as axicabtagene ciloleucel and tisagenlecleucel, particularly in patients with relapsed or refractory B-cell malignanciesn [13]. For example, in acute lymphoblastic leukemia (ALL), CD19-directed CAR-T cell therapies have achieved complete remission rates of up to 90% in some patient groups who no longer respond to conventional chemotherapy [13]. This high efficacy is partly due to the ability of CAR-T cells to persist in the patient's body for an extended period, providing long-term surveillance and protection against relapse [12]. Other clinical trials involve the use of CAR-T cells engineered to recognise and attack the GD2 antigen overexpressed in neuroblastoma cells. In particular, GD2 is a disialoganglioside that serves as a promising target for CAR-T therapy due to its limited expression on normal tissues and its high prevalence on the surface of neuroblastoma cells [14]. Findings from trials have demonstrated that the use of GD2-targeted CAR-T cells is both feasible and safe, though efficacy remains limited. Researchers have identified immune determinants, such as the presence of naïve T-cells and CXCR3+ monocytes in pre-treatment apheresis, which play a crucial role in CAR-T cell expansion and patient outcomes [14].

However, alongside these achievements, CAR-T therapy is also associated with serious side effects, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which arise due to excessive immune activation [4]. Additionally, it has been an emerging concern that the patients treated with CAR-T therapy are suffering the risk of secondary malignancies, especially T-cell lymphomas [15]. Despite these challenges, the current research focus is on expanding the application scope and improving the safety of CAR-T therapy. At

present, researchers are exploring the combination of CAR-T cells and checkpoint inhibitors or oncolytic viruses as a strategy to overcome the immunosuppressive tumour microenvironment [13].

3.2. TCR-T Cell Therapy

T-cell receptor-engineered T cells (TCR-T cells) represent a promising frontier in cancer immunotherapy, working by genetically engineering T cells to express specific TCRs that can recognise tumour-associated antigens presented by the major histocompatibility complex (MHC). This mechanism enables TCR-T cells to target both cell-surface and intracellular antigens and a wider range of tumor antigens, including neoantigens and tumor-specific mutated proteins, providing greater versatility in attacking tumours [1]. Recently, new innovations include engineering TCR-T cells with additional cytokine receptors to enhance their proliferation, differentiation, and anti-tumour activity. For example, Interleukin-21 (IL-21) receptor-armed TCR-T cells have shown increased ability against hepatocellular carcinoma (HCC) by reducing cell exhaustion and apoptosis under sustained antigen exposure [16].

Compared with CAR-T cells, which recognise only cell-surface antigens such as CD19 or BCMA, the TCR-T cells gain access to the entire cellular proteome of the cancer cell through interaction between TCR and MHC. This capability is crucial for treating solid tumors that often express intracellular or mutated antigens unavailable to CAR-T cells. In addition, on the contrary with CAR-T cells which are limited to recognising unmutated and cell-surface antigens, TCR-T cells are designed to recognise neoantigens derived from tumor-specific mutations that are not found in normal tissues. This gives TCR-T therapy an advantage in selectively targeting tumour cells while minimising off-target effects [1]. However, the effectiveness of TCR-T therapy can be influenced by a patient's specific human leukocyte antigen (HLA) profile due to the MHC-dependent property of TCR-T cells, while CAR-T cells are designed to target cell-surface markers without MHC involvement. This limitation necessitates personalised modifications in TCR-T therapy based on HLA compatibility in a complicated standardisation [17].

Several clinical trials have demonstrated the efficacy of TCR-T therapy in combating solid tumours. For example, in a phase II trial carried out by [18], TCR-transduced cells that express personalised neoantigen-reactive TCRs were transferred into metastatic colorectal cancer patients who were previously treated by multiple therapies. As a result, these genetically modified T cells exerted strong tolerance and led to significant tumour regression, with responses lasting several months. Another evidence of TCR-T potential in tumour treatment is the FDA approval of Tecelra (Afamitresgene autoleucel) for synovial sarcoma, which made it the first engineered TCR-T cell therapy approved for a solid tumour. In detail, the way of Tecelra treating advanced synovial sarcoma is specifically targeting a highly immunogenic antigen called melanoma- associated antigen A4 (MAGE-A4) [19]. In addition, this essential cancer-testis antigen acts as an ideal target of TCR-T cells due to its characteristically selective expression that is massive in tumours compared with normal cells. This MAGE-A4-targeted TCR-T cell therapy has been validated through two clinical trials, where this approach exerted high potential in combating different solid cancers beyond sarcoma [1]. Moreover, combining TCR-T cell therapy with other immunotherapies including checkpoint inhibitors and PD-1 antagonists has shown the potential to amplify anti-tumour responses. Checkpoint inhibitors work by removing the brakes on T cells, activating them to attack cancer more effectively, while TCR-T cells deliver precise targeting of tumour antigens [1, 17].

Despite its advantageous potential in clinical applications, TCR-T cell therapy still faces several challenges. First of all, this treatment is extremely costly for many patients due to its biotechnological complexity and personalised design. In addition, tumour cells are genetically and phenotypically various even within the same patient, conferring huge heterogeneity that leads to fluctuated effectiveness against all tumorous cells. To address this uncertainty, drastic analysis and clinical data of how TCR-T cell therapy acts on different cancers are significant but time-consuming and currently inadequate [1]. Another limitation of TCR-T cell therapy is the risk of unexpected targeting. To be specific, since TCR-T cells recognise antigens presented by MHC molecules, there is a risk that they

might also attack normal tissues expressing the same antigens even at low levels. This has led to severe side effects in clinical trials, such as cardiotoxicity in patients treated with TCR-T cells targeting MAGE-A3 and colitis in patients receiving CEA-targeted therapy. Prevention of these cases requires meticulous antigen selection and rigorous preclinical testing to minimise cross-reactivity [17]. Moreover, immunosuppressive tumour microenvironment (TME) is a substantial barrier to the application of TCR-T therapy. The TME in solid tumours often includes excessive regulatory T cells (Tregs) and immunosuppressive cytokines such as transforming growth factor-beta (TGF-β), which inhibit the activity of TCR-T cells [20]. An example caused by TME is the vasculature barrier of stroma, where the access of TCR-T cells to the tumour is restricted in hepatocellular carcinoma patients. To overcome this, researchers investigated transducing the signal of the IL-21 receptor to TCR-T cells, which promotes their proliferation and memory to defeat the degradation of TCR-T cells under TME [16]. Lastly, predicting patient responses to TCR-T therapy remains an ongoing challenge due to the heterogeneity of tumours and variations in antigen presentation. To address this, some mathematical models have been developed to simulate immune-tumour interactions and identify the key parameters influencing TCR-T cell effectiveness. These models help researchers have a better understanding of dynamic and complex tumour environments, which contributes to refining treatment strategies [20].

3.3. Other Genetically Modified Immune Cells and Their Implications

Beyond the CAR-T and TCR-T cell therapies, other genetically modified immune cells are emerging as powerful approaches in cancer immunotherapy. For instance, natural killer (NK) cells are potential candidates due to their intrinsic cytotoxicity and cytokine responses against tumour cells. Compared to T cells, antigen priming is unnecessary for NK cell actions as an innate immune response, making NK cells less prone to severe side effects such as cytokine release syndrome and neurotoxicity. However, under tumour microenvironment, these conventional NK cells exhibit deficiencies in tumour infiltration and antigen recognition, which can be addressed by genetic engineering. On the one hand, naked NK cells armed with chimeric antigen receptors (CAR-NK) are conferred the ability of recognising the specific tumour antigens in an MHC-independent way, eliciting activation signal which enhance tumour cell killing and cytokine production. On the contrary, non-CAR NK cells are the result of knocking out the inhibitory genes involved in NK cell-based immune response, using gene editing tools such as CRISPR/Cas-9 and Zinc finger nucleases. These approaches significantly enhance NK cell's targeting capabilities, persistence, and infiltration in tumours. [21]. Concurrently, mesenchymal stromal cells (MSCs) characterised by their tumour-homing properties are being genetically modified to deliver therapeutic molecules such as interleukins (ILs) and interferons (IFNs). These cytokine-engineered MSCs help bolster localised immune responses and minimise systemic toxicity, which is a potentially safe approach to cancer therapy [22].

In addition, innovative nanotechnology has been recently applied for genetically engineered cytomembrane nanovaccines and exosome-based therapies. For example, PD1/CD40L Nanovesicles (PD1/CD40L-NVs) are genetically engineered nanovesicles that overexpress the immune checkpoint inhibitor PD1 and the co-stimulatory molecule CD40L at the same time. Therefore, PD1/CD40L-NVs are able to block the PD-1/PD-L1 signalling pathway while activating dendritic cells to stimulate robust T-cell-mediated antitumor immunity. This synergistic action improves immune checkpoint blockade (ICB) therapies due to increased cytotoxic T-cell infiltration in the tumour microenvironment. In addition, this nanovaccine formula shows enhanced lymph node trafficking and retention since it uses cancer cell membranes to mimic natural cellular interactions with immune cells in lymph nodes, which ultimately boosts the effectiveness of the immune response against tumours [23]. Similarly, engineered exosomes derived from immune cells are utilised as biological nanocarriers for delivering drugs and immune-stimulating molecules, which are achieved by genetic modifications of their parental immune cells. Then, these engineered cells are able to produce the desired proteins, receptors or signalling molecules, which are incorporated into exosomes. This

strategy increases the delivery efficiency and targeting ability of exosomes and strengthens both innate and adaptive immune responses against cancers [24].

4. Synergistic Therapy Utilising Armed Antibodies and Genetically Modified Immune Cells

4.1. Principles and Clinical Trials of Synergistic Therapy

Synergistic cancer therapy combines different cancer treatment strategies to improve therapeutic efficacy and reduce drug resistance. This has been exemplified by the cooperation of antibody-drug conjugates (ADCs) and genetically modified immune cells (CAR-T or TCR-T cells). ADCs deliver cytotoxic agents directly to tumour cells, while engineered immune cells strengthen the immune system's ability to recognise and destroy cancer cells, creating a more comprehensive attack. ADCs bind to specific tumour antigens, releasing cytotoxic drugs to reduce tumour burden, while CAR-T cells target and eliminate residual cancer cells that may evade ADCs. This dual action ensures the destruction of larger amount of tumour cells than using each of the therapies alone [3].

A key advantage of this combination is its ability to reduce tumour resistance. By utilising distinct mechanisms—cytotoxic delivery by ADCs and immune-mediated targeting by CAR-T cells—the therapy lowers the chance of cancer cells adapting and developing resistance [25, 26]. Additionally, ADCs often induce immunogenic cell death (ICD), releasing tumour-associated antigens (TAAs) that activate CAR-T cells and amplify the immune response. This process recruits additional immune cells, resulting in a robust and sustained defence against the tumour [3]. The combination also alters the tumour microenvironment (TME), which is typically immunosuppressive. ADCs eliminate immune-suppressive cells, making the TME more conducive to CAR-T cell activity. In turn, CAR-T cells release cytokines like IL-2 and IFN-γ, further boosting immune function [26]. By addressing tumour heterogeneity, the dual targeting of ADCs and CAR-T cells applies selective pressure across a broader range of cancer cells, reducing tumour escape and leading to more durable outcomes [3].

Recent clinical trials have increasingly focused on combining antibody-based therapies with CAR-T cell treatments, particularly in cancers like CD30+ lymphomas. For instance, brentuximab Vedotin is an antibody-drug conjugate that has been combined with CD30-directed CAR-T cells. The experimental results show significantly enhanced antitumor efficacy. This combination has also shown remarkable improvements in objective response rates (ORR) and overall survival (OS) compared to any single approach. Additionally, in some clinical trials, immune checkpoint inhibitors (ICIs) were integrated with armed antibodies and CAR-T cells, which can further amplify the immune response and prevent T-cell exhaustion, thereby improving the durability and effectiveness of the treatment [3].

4.2. Advantages and Challenges of Synergistic Therapy

The combination of armed antibodies and genetically modified immune cells offers several key advantages in cancer treatment. This synergistic approach enhances efficacy by amplifying tumour cell killing through coordinated mechanisms, including antigen release, improved immune infiltration, and the joint action of both therapies [3]. The release of tumour-associated antigens (TAAs) from armed antibodies primes genetically modified immune cells, helping create a robust and long-lasting immune memory response that enhances the overall treatment effect [26].

However, this approach also presents challenges. First, the combined therapies can lead to excessive immune activation, increasing the risk of side effects such as cytokine release syndrome (CRS) and neurotoxicity [3, 26]. Additionally, the production and delivery of these therapies involve complex manufacturing processes, which increase costs and limit accessibility [25]. Despite these, the synergistic combination is still considered a promising approach in cancer immunotherapy, which addresses tumour heterogeneity and provides more personalised treatments.

5. Conclusion

In summary, the integration of armed antibodies and genetically modified immune cells represents a transformative development in cancer therapy, providing a powerful combination of precision and adaptability in fighting a wide range of tumour types. Antibody-drug conjugates (ADCs), or armed antibodies, merge the specificity of monoclonal antibodies with potent cytotoxic drugs to be delivered precisely to the tumour site while minimising damage to surrounding healthy cells. Compared to conventional cancer treatment methods, this targeted approach ensures that the toxic components on the antibody are not easily separated before entering the human cancer cell, so the risk of transmission of 'toxicity' in the blood is lower, and there are fewer side effects.

Genetically modified immune cells, especially CAR-T and TCR-T cells, further enhance tumour recognition and cytotoxicity through genetic engineering that reprograms immune cells to target cancer-specific antigens. For example, CAR T cell therapy has been remarkably successful in treating cancers of blood diseases, while TCR-T cell therapy offers new hope for treating solid tumours by utilising intracellular targets. However, these therapies face significant challenges, including side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxic syndrome (ICANS).

The combination of ADCs with CAR-T or TCR-T cells is an innovative strategy that exerts better therapeutic consequences than each single approach. This dual approach utilises the cytotoxic precision of ADCs to remove tumours and release tumour-associated antigens (TAAs), which then activate CAR-T cells, sustaining a robust and ongoing immune response. By addressing the unique challenges of tumour heterogeneity and drug resistance, this combination approach not only improves efficacy persistence but also reduces the probability of cancer recurrence.

Despite these advances, challenges remain for widespread clinical application. For example, due to high production costs, limited accessibility, and the risk of serious immune-related side effects, researchers need to conduct ongoing research to improve and simplify these therapies to make them more actionable and affordable. However, as ADCs and genetically modified immune cells continue to evolve, they promise to redefine the landscape of cancer immunotherapy, bringing us closer to the goal of personalised, effective, and long-lasting cancer treatments. This combined approach represents a new frontier in precision medicine, with the potential to significantly improve outcomes for cancer patients worldwide.

Reference

[1] Li, J., Zhang, Y., Fu, T., Xing, G., Cai, H., Li, K. Q., & Tong, Y. (2024). Clinical advances and challenges associated with TCR-T cell therapy for cancer treatment. Frontiers in Immunology, 15, 1487782.

[2] Luo, J., & Zhang, X. (2024). Challenges and innovations in CAR-T cell therapy: a comprehensive analysis. Frontiers in Oncology, 14.

[3] Chang, Y., Chang, M., Bao, X., & Dong, C. (2024). Advancements in adoptive CAR immune cell immunotherapy synergistically combined with multimodal approaches for tumor treatment. Bioactive Materials, 42, 379-403.

[4] Zhou, Z., Zhang, G., Xu, Y., Yang, S., Wang, J., Li, Z. ... & Lu, Q. (2024). The underlying mechanism of chimeric antigen receptor (CAR)-T cell therapy triggering secondary T-cell cancers: Mystery of the Sphinx? Cancer Letters, 597, 217083.

[5] Abuhelwa, Z., Alloghbi, A., & Nagasaka, M. (2022). A comprehensive review on antibody-drug conjugates (ADCs) in the treatment landscape of non-small cell lung cancer (NSCLC). Cancer Treatment Reviews, 106, 102393.

[6] López de Sá, A., Díaz-Tejeiro, C., Poyatos-Racionero, E., Nieto-Jiménez, C., Paniagua-Herranz, L., Sanvicente, A., & Ocana, A. (2023). Considerations for the design of antibody drug conjugates (ADCs) for clinical development: lessons learned. Journal of Hematology & Oncology, 16(1), 118.

[7] Esapa, B., Jiang, J., Cheung, A., Chenoweth, A., Thurston, D. E., & Karagiannis, S. N. (2023). Target antigen attributes and their contributions to clinically approved antibody-drug conjugates (ADCs) in haematopoietic and solid cancers. Cancers, 15(6), 1845.

[8] Marei, H. E., Cenciarelli, C., & Hasan, A. (2022). Potential of antibody–drug conjugates (ADCs) for cancer therapy. Cancer Cell International, 22(1), 255.

[9] Hong, J., Li, K., He, J., & Liang, M. (2024). A New Age of Drug Delivery: A Comparative Perspective of Ferritin–Drug Conjugates (FDCs) and Antibody–Drug Conjugates (ADCs). Bioconjugate Chemistry, 35(8), 1142-1147.

[10] Dri, A., Arpino, G., Bianchini, G., Curigliano, G., Danesi, R., De Laurentiis, M., & Puglisi, F. (2023). Breaking barriers in triple negative breast cancer (TNBC)–Unleashing the power of antibody-drug conjugates (ADCs). Cancer Treatment Reviews, 102672.

[11] Tao, R., Han, X., Bai, X., Yu, J., Ma, Y., Chen, W., & Li, Z. (2024). Revolutionizing cancer treatment: enhancing CAR-T cell therapy with CRISPR/Cas9 gene editing technology. Frontiers in Immunology, 15, 1354825.

[12] Cordas dos Santos, D. M., Tix, T., Shouval, R., Gafter-Gvili, A., Alberge, J. B., Cliff, E. R. S., & Rejeski, K. (2024). A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. Nature medicine, 30(9), 2667-2678.

[13] Uslu, U., Castelli, S., & June, C. H. (2024). CAR T cell combination therapies to treat cancer. Cancer Cell, 42(8), 1319-1325.

[14] Hamilton, M. P., Sugio, T., Noordenbos, T., Shi, S., Bulterys, P. L., Liu, C. L., & Miklos, D. B. (2024). Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy. New England Journal of Medicine, 390(22), 2047-2060.

[15] Ghilardi, G., Fraietta, J. A., Gerson, J. N., Van Deerlin, V. M., Morrissette, J. J., Caponetti, G. C., ... & Ruella, M. (2024). T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. Nature Medicine, 1-6.

[16] Zhu, W., Zhang, Z., Chen, J., Chen, X., Huang, L., Zhang, X., & Hou, J. (2024). A novel engineered IL-21 receptor arms T-cell receptor-engineered T cells (TCR-T cells) against hepatocellular carcinoma. Signal Transduction and Targeted Therapy, 9(1), 101.

[17] Golikova, E. A., Alshevskaya, A. A., Alrhmoun, S., Sivitskaya, N. A., & Sennikov, S. V. (2024). TCR-T cell therapy: current development approaches, preclinical evaluation, and perspectives on regulatory challenges. Journal of Translational Medicine, 22(1), 897.

[18] Parkhurst, M., Goff, S. L., Lowery, F. J., Beyer, R. K., Halas, H., Robbins, P. F., & Rosenberg, S. A. (2024). Adoptive transfer of personalized neoantigen-reactive TCR-transduced T cells in metastatic colorectal cancer: phase 2 trial interim results. Nature Medicine, 30(9), 2586-2595.

[19] Harrison, C. TCR cell therapies vanquish solid tumors—finally. Nature biotechnology.

[20] Wang, Z., Cho, H., Choyke, P., Levy, D., & Sato, N. (2024). A Mathematical Model of TCR-T Cell Therapy for Cervical Cancer. Bulletin of Mathematical Biology, 86(5), 57.

[21] Maia, A., Tarannum, M., & Romee, R. (2024). Genetic manipulation approaches to enhance the clinical application of NK cell-based immunotherapy. Stem Cells Translational Medicine, 13(3), 230-242.

[22] Švajger, U., & Kamenšek, U. (2024). Interleukins and interferons in mesenchymal stromal stem cell-based gene therapy of cancer. Cytokine & Growth Factor Reviews.

[23] Pan, Y., Wu, X., Liu, L., Zhao, C., Zhang, J., Yang, S., & Rao, L. (2024). Genetically Engineered Cytomembrane Nanovaccines for Cancer Immunotherapy. Advanced Healthcare Materials, 2400068.

[24] Jung, I., Shin, S., Baek, M. C., & Yea, K. (2024). Modification of immune cell-derived exosomes for enhanced cancer immunotherapy: current advances and therapeutic applications. Experimental & Molecular Medicine, 56(1), 19-31.

[25] Abd El-Hafeez, T., Shams, M. Y., Elshaier, Y. A., Farghaly, H. M., & Hassanien, A. E. (2024). Harnessing machine learning to find synergistic combinations for FDA-approved cancer drugs. Scientific Reports, 14(1), 2428.

[26] Looi, C. K., Loo, E. M., Lim, H. C., Chew, Y. L., Chin, K. Y., Cheah, S. C., ... & Mai, C. W. (2024). Revolutionizing the treatment for nasopharyngeal cancer: the impact, challenges and strategies of stem cell and genetically engineered cell therapies. Frontiers in Immunology, 15, 1484535.