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Revolutionizing the treatment of cancer using CAR T Cells and Bispecific Antibodies

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Abstract: Zinc is one of the most crucial trace minerals that is needed for human health and development. This study was conducted to assess zinc concentrations in breast milk samples obtained from Palestinian lactating women. The study also aimed to assess associations between breast milk zinc concentrations, dietary zinc intake, and signs and symptoms of zinc deficiency. Breast milk samples were obtained from 58 lactating women. The demographic variables, dietary zinc intake, and signs and symptoms of zinc deficiency were also collected. Zinc concentrations were assessed using a graphite furnace atomic absorption spectrophotometric method. Of the lactating women, 7 (12.1%) reported loss of appetite, 6 (10.3%) reported sleepiness or lethargy, 11 (19.0%) reported changes in weight, 7 (12.1%) reported increasing hair loss, 8 (13.8%) reported having easily broken nails, 7 (12.1%) reported having immune diseases/issues, and 11 (19.0%) reported dermatologic issues. In this study, 21 (36.2%) of the lactating women reported high consumption of red meats or poultry, 22 (37.9%) reported high consumption of milk or dairy products, 19 (32.8%) reported high consumption of whole grains, 18 (31.0%) reported high consumption of fish or seafood, 12 (20.7%) reported high consumption of eggs, and 9 (15.5%) reported high consumption of zinc-rich drinks. In this study, the median breast milk zinc level was 0.091 [0.063, 0.15] mg/100 mL. Breast milk zinc concentrations were higher among the lactating women who were younger than 30 years, lived in urban areas, were employed, and reported high consumption of zinc-rich drinks. Breast milk zinc concentrations were affected by some demographic variables of the lactating women. These variables included, demographics, living conditions, and consumption of zinc-rich sources. Dieticians, lactation consultants, and other healthcare providers should educate/counsel lactating women on the importance of maintaining adequate breast milk zinc levels and consuming zinc-rich sources. More studies are still needed to assess the impact of zinc supplements on breast milk zinc concentrations.

Keywords: CAR T cell therapy, Bispecific Antibody therapy, Immunotherapy, CD19 CAR T Cells, Immune Check Point Inhibitors, FDA-approved therapies, Advancement in Cancer Therapy.

INTRODUCTION

Recent advancements in cancer therapy have shifted the focus from traditional methods like surgery, chemotherapy, and radiotherapy to immunotherapy, especially CAR T cell therapy. This approach uses genetically modified T cells with Chimeric Antigen Receptors (CARs) to target cancer cells independently of the Major Histocompatibility Complex (MHC) [1]. Proven effective in chemotherapy-resistant B-cell malignancies [2], CAR T cell therapy achieves notable remission rates. Its efficacy is underpinned by Adoptive Cell Transfer (ACT), wherein patients receive immunocompetent cells to target and destroy cancer cells, bypassing the constraints of conventional vaccine-based therapies [3].

In parallel, newer immunotherapies like bispecific T-cell enhancing antibodies and monoclonal antibodies against immune checkpoints CTLA-4 and PD-1 are showing promise across diverse cancer types [4-5]. CAR T cell therapies are particularly potent in blood cancers due to their self-amplifying and persistent nature. However, their effectiveness against solid tumours is still under investigation [3]. Recent trials in multiple myeloma treatment with CAR T cells are encouraging [6-7]. Another innovative approach is the use of Bispecific antibodies (BsAbs), which can target two antigens simultaneously. BsAbs are crucial in liquid tumours, like leukaemia's and lymphomas, enhancing the precision of immunotherapy by linking immune cells to cancer cells [8-9]. They also show potential against solid tumours by disrupting the immunosuppressive tumour microenvironment, improving tumour cell detection and elimination. Yet, optimization of BsAbs is necessary which involves a multifaceted approach encompassing improvements in specificity, binding affinity, immunogenicity, pharmacokinetics, tumour penetration, and resistance prevention for enhanced effectiveness [10]. Their dual-targeting ability marks a significant breakthrough in cancer immunotherapy, potentially reducing the dosage of therapeutic antibodies.

To conclude, CAR T cell therapy and bispecific antibodies have revolutionized cancer treatment [13-14]. CAR T cells are particularly effective against B-cell malignancies but face challenges in solid tumours. Bispecific antibodies, conversely, target both liquid and solid tumours innovatively. These therapies signify a shift towards more personalized, effective cancer treatments, emphasizing the reprogramming of T cells and connecting immune cells to tumour cells. Continuous

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research and development are crucial, but their synergistic potential heralds a new, more targeted era in cancer therapy.

CAR T cell therapy

Origin and Development

Immunotherapy has significantly advanced cancer treatment, offering hope to patients with cancer. The foundation for CAR T cell therapy was laid in 1987 by Dr. Yoshikazu Kurosawa and his team at Japan's Institute for Comprehensive Medical Science. They introduced the concept of a chimeric T cell receptor combining antibody-derived variable regions (VH/VL) with T cell receptor (TCR)-derived constant regions. Their study showed that these receptors, when expressed in murine T-cell lymphoma EL4 cells, could trigger a response to antigens, marking a significant breakthrough in understanding the immune system's role in combating cancer [11]. In 1989, Israeli immunologist Zelig Eshhar proposed reprogramming T cells to recognize antigens independently of the major histocompatibility complex (MHC). This concept led to the development of Chimeric Antigen Receptors (CARs) in the early 2000s. CARs revolutionized cancer immunotherapy by enabling T cells to target specific tumour antigens. This breakthrough has transformed cancer treatment, illustrating the impact of foundational research on medical innovation [12]. They developed a chimeric T-cell receptor (cTCR) fusing the variable regions of an anti-2,4,6-trinitrophenyl (TNP) antibody with TCR constant regions. This innovation allowed T cells to recognize antigens independently of MHC molecules, a crucial step forward. Eshhar's team overcame initial challenges of low co-transduction efficiency by creating a single-chain chimeric receptor, the first-generation CAR, linking the scFv antigen-binding domain to an intracellular signalling domain. This design preserved the specificity and affinity of the original antibody [13].

Initial clinical applications in 2005 for metastatic renal cell carcinoma and ovarian cancer revealed safety concerns and uncertain therapeutic benefits [11]. However, the landscape changed dramatically with the introduction of anti-CD19 CAR T cells, which demonstrated remarkable efficacy in treating lymphomas and leukaemia. These successes at the NCI and the University of Pennsylvania marked a pivotal point in the therapy's evolution [1]. The development of CAR T cell therapy in the USA catalysed its global expansion, underscoring the vital contributions of these early studies to the field of immunotherapy [14]. CAR T cell therapy, a revolutionary cancer treatment, utilizes engineered T-cells with Chimeric Antigen Receptors (CARs). These receptors target tumour cells with high specificity. A CAR comprises an extracellular antigen recognition domain, a transmembrane domain, and an intracellular T cell activation domain, combining precision targeting with effective immune response [15-16].

The extracellular domain begins with a signal peptide, leading the protein into the endoplasmic reticulum, followed by an antigen recognition section. This section includes a single-chain Fragment variant (scFv), formed by linking heavy and light immunoglobulin chains [16-17]. A spacer, typically from the IgG1 hinge region, connects this to the transmembrane domain, which is vital for receptor stability and commonly uses the CD28 transmembrane domain [15-17]. The intracellular domain, primarily comprising the CD3ζ component, is critical for initiating T cell responses upon antigen detection, thus playing a pivotal role in activating the immune response against cancer cells [16]. CAR T cell technology has evolved significantly since the first-generation CARs developed between 1989 and 1993, which had limited efficacy without additional IL-2 [18-19]. Subsequent generations have seen improvements in T-cell antitumor activity and in vivo persistence. Notably, the fourth-generation CARs, known as TRUCKs, have elevated antitumor efficacy and cytokine activity [14]. Research in CAR T cell therapy is continually evolving. Techniques such as CRISPR and the development of smart T cells are being explored to enhance safety and efficacy [20-23]. The optimal mix of costimulatory signals, including CD28 [14], ICOS, OX40, and 4-1BB, is an area of active research, with 4-1BB showing promise in improving CAR T cell persistence [25-27].

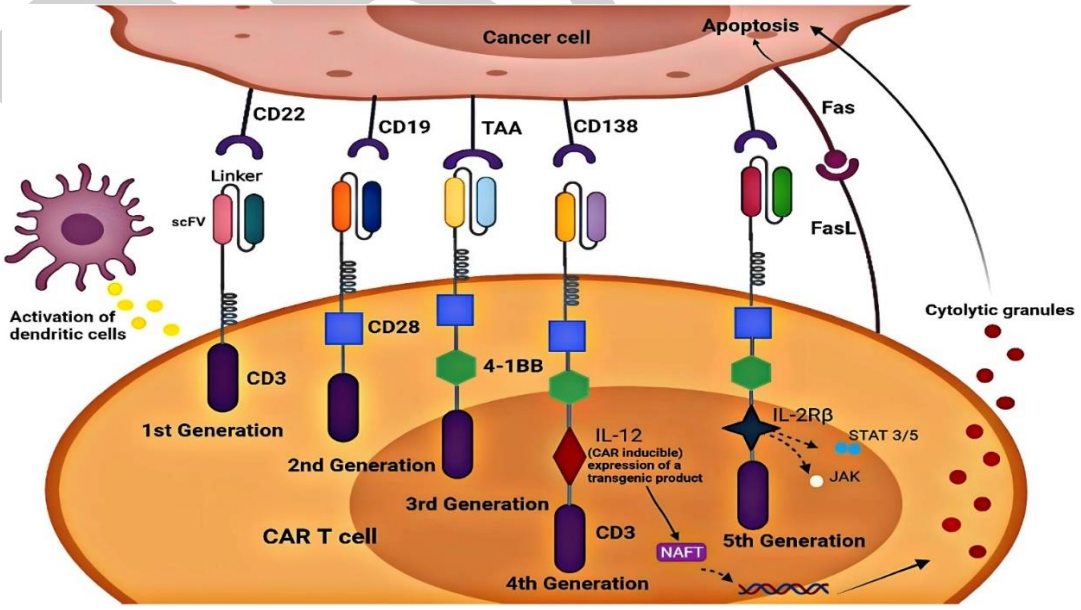
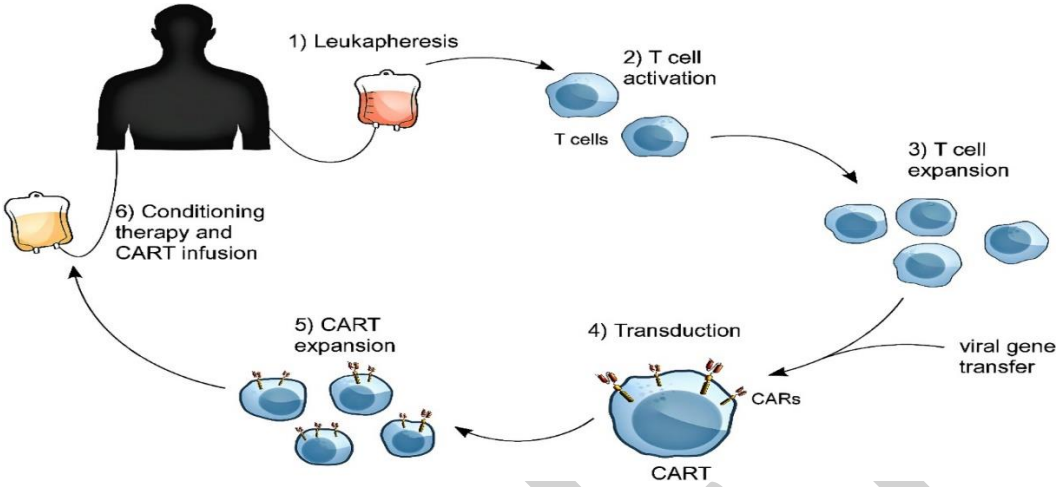


Figure (1): Details the structural progression across five CAR T cell generations and their targets on tumour cells. The first-generation focuses on the CD3ζ component. The second and third generations introduce and combine additional signalling elements like CD28 and 4–1BB. Fourth-generation CARs, or TRUCKs, incorporate genetic modifications for enhanced cytokine secretion. The fifth generation adds a novel intracellular domain, including truncated cytokine receptor domains, to further refine targeting and effectiveness (A Z Mehrabadi et al., Biomedicine& Pharmacotherapy 2022,146) [28].

Engineering CAR T cells, target recognition and tumour cell killing

CAR T cell therapy, a ground-breaking treatment, stands out for its self-replicating and persistent nature in patients. This process, depicted in Figure 2, starts with isolating T cells from the patient or a donor's blood. These cells are then activated and genetically altered to express the CAR construct [14]. After this modification, the CAR T cells undergo expansion outside the body, leading to the formation of the final therapeutic product. The patient typically receives this product via infusion after conditional chemotherapy [14].



As shown in Figure 2, the initial step of CAR T cell generation involves harvesting immune cells through leukapheresis. Post-harvesting, T cells are isolated, activated, expanded, and then undergo gene transfer via a viral vector to express CARs. To increase the quantity of these modified T cells, they are cultivated in a bioreactor. Finally, they are harvested and infused into the patient, usually following lymphodepletion conditioning chemotherapy (KatarzynaS et al., Archivum Immunologiae et Therapiae Experimentalis 2020,68[6])[29].

CAR T cells are classified as autologous, derived from the patient's own blood, or allogeneic, obtained from a healthy donor. Regardless of their source, these cells are engineered to express an artificial T cell receptor, enabling them to target disease-related cells without relying on Major Histocompatibility Complex (MHC) engagement [14]. CARs are synthetic proteins designed to direct T cells toward tumour cell surface molecules, independent of T cell receptor (TCR) - MHC interactions [30-31]. Introduced typically via gene transfer, CARs incorporate a mouse-derived monoclonal antibody-based single-chain variable fragment (scFv) for antigen recognition. These scFvs, connected by an extracellular spacer, bind to specific epitopes and trigger activation signals through intracellular domains [32]. Once introduced to peripheral blood-derived T cells and expanded in culture, these CAR T cells are used to detect and eliminate tumour cells expressing the target antigen [33-34]. Targeting a broad spectrum of tumour cell surface molecules, including proteins, carbohydrates, and glycolipids, is a key feature of CARs. The interaction between CAR and its target creates immune synapses, leading to direct cytotoxicity against tumour cells. The effectiveness of this approach hinges on the selected antigen being abundantly present on the tumour cells [35].

CARs are engineered constructs that bind specific cell surface antigens, using a scFv for recognition [36]. The initial generation of CARs fused a ligand recognition domain with the CD3 zeta (3ζ) chain, comprising an extracellular hinge and a transmembrane domain. This design enables the CD3ζ chain to autonomously signal T cell activation via phosphorylation of ITAMs by the lymphocyte-specific protein tyrosine kinase (Lck). Later generations of CARs incorporated additional signalling endodomains, such as CD28, CD137 (4-1BB), and inducible T cell co-stimulator (ICOS), to mimic antigen-presenting cells' co-stimulatory signals during T cell receptor engagement [37]. Advanced CAR T cells, like the fourth and fifth generations, include cytokine receptor domains and induce inflammatory cytokines, like interleukin-12 (IL-12) or IL-18, enhancing their efficacy against both solid and liquid tumours.

Clinical applications

The evolution of anti-cancer therapy has historically relied on four primary treatments: surgery, radiation, chemotherapy, and immunotherapy. A notable advancement occurred at the University of Pennsylvania and Children's Hospital in Philadelphia, where researchers Carl June, David Porter, and Stephan Grupp pioneered CAR T cell therapy in 2011 and 2012. Initially applied to chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL), this approach has shown significant success over the past decade, especially in treating B cell ALL and non-Hodgkin lymphoma (NHL) [18, 38-40]. CAR T cells, which are genetically modified autologous T cells equipped with chimeric antigen receptors, excel at recognizing cell surface epitopes without HLA dependence. They are designed to specifically bind to antigens like CD19 and feature optimized T cell activation and co-stimulatory domains [41]. Recent advances in CAR-T therapy signify a new era in cancer treatment, demonstrating substantial progress in hematologic malignancies, including lymphoma and leukemia, and showing promising results in solid tumours like glioblastomas and neuroblastoma [42]. Additionally, adapting chimeric antigen receptors to natural killer (NK) cells is emerging as a potential cellular immunotherapy approach, effective in targeting cancer cells [43].

CAR T cell therapy is under active investigation for solid tumours and various diseases. For instance, mesothelin-specific CAR mRNA-engineered T cells show potential against solid malignancies [44]. Novel applications, such as HLA-A2-specific CARs, are being explored in organ transplants [45] and

preclinical studies for targeting the 5T4 tumour antigen in ovarian cancer [46]. A key advantage of CAR T cell therapy is its rapid administration, typically involving a single infusion and requiring only 2–3 weeks of patient observation. This approach facilitates long-term CAR T cell persistence in the body, combatting cancer relapse effectively [47-48]. FDA-approved therapies like CTL019 (Kymriah), KTE-C19 (Yescarta), and JCAR015, which target CD19, are examples of successful CAR T cell treatments on the market [49-52]. As of April 2023, six approved CAR T cell therapies have shown remarkable efficacy against B-cell malignancies and multiple myeloma [13].

However, applying CAR T cell therapy to solid tumours presents unique challenges, with responses not as robust as those seen with CD19 CAR T cells [53]. Solid tumours create complex obstacles, such as genetic instability, hindered CAR T cell trafficking, and immunosuppressive microenvironments. Additionally, "on-target off-tumour" reactions can cause rapid adverse effects [54]. To overcome these challenges, innovative strategies are being developed, including inhibitory CARs (iCARs) and logic-gated CARs [55]. Enhancing CAR T cell performance can also be achieved by incorporating chemokine receptor genes that match tumour-produced chemokines, like CCR2b in CCL2-secreting neuroblastoma cells, and by arming CAR T cells with enzymes like heparinase to degrade the basement membrane [56]. Combining CAR T cell therapy with immunomodulatory agents such as checkpoint inhibitors, cytokines, and small-molecule antagonists is another approach showing potential for synergistic antitumor responses [57].

Efficacy and safety

Research on CAR T cell therapy, a ground-breaking cancer treatment, started almost twenty years ago. Initially, trials targeted ovarian cancer and renal cell carcinoma. Remarkable results were observed in some patients with neuroblastoma and follicular lymphoma. By 2016, the volume of clinical trials expanded significantly to 220, primarily in the USA and China, with an emphasis on treating blood cancers [14, 58]. A major advancement occurred with the FDA's approval of Cellectis' UCART123 for allogenic CAR T cell trials, which use donor-derived cells [59-60]. In trials for CD19 CAR T cells, which are engineered to attack cancer cells expressing the CD19 protein, 67% of acute lymphoblastic leukemia (ALL) patients and 82% of non-Hodgkin lymphoma (NHL) patients showed a positive response. At 9 months, 40% of ALL patients maintained this response. However, these promising results came with serious side effects like cytokine release syndrome (CRS) and neurotoxicity, which significantly affected patient health [61-62]. CRS leads to an overwhelming release of cytokines, causing symptoms such as high fever and low blood pressure. Treatment strategies for these side effects include the use of tocilizumab and intensive care support. Still, the recurrence rate remains high, with over half of the patients experiencing cancer return, and 30-50% relapsing within a year [62]. The challenges in treating patients without CD19 expression and those with solid tumours highlight the need for new approaches in B cell cancer therapies [63]. CAR T cell therapy can also cause severe CRS, leading to symptoms like fever, chills, and breathing difficulties [64]. With increasing experience, healthcare professionals are improving in both detecting and managing CRS. Neurological issues, including headaches, confusion, seizures, and speech problems — collectively known as immune effector cell–associated neurotoxicity syndrome (ICANS) — are also prevalent, though their exact cause is not yet fully understood [64]. Other side effects of CAR T cell therapy include allergic reactions, changes in blood mineral levels, weakened immunity, increased infection risk, low blood cell counts, fatigue, and bruising [65]. A critical condition, tumour lysis syndrome (TLS), can arise from rapid cancer cell breakdown following therapy or lymphodepleting chemotherapy, potentially causing arrhythmias and renal failure. Preventive measures for TLS in patients with high tumour burdens include adequate hydration and the use of hypouricemic agents [66-70].

Future directions

CAR T therapy, known for its impressive treatment outcomes, faces challenges such as limited response durability, leading to relapse rates as high as 66% [71]. Addressing this, recent advancements in immunology and molecular engineering have led to the development of next-generation CAR T cells. These incorporate diverse mechanisms, including additional costimulatory domains, cytokine secretion induction, and immune checkpoint modulation. These strategies aim to enhance malignant cell elimination [71-73]. Third-generation CAR T cells show variable efficacy, but immune checkpoint modulation, particularly in PD-L1 malignancies, has achieved response rates up to 78% [74-75]. Similarly, TRUCK CAR T cells, which utilize cytokines, have shown promising yet varied response rates, ranging from 0% to 100% [31, 76-78]. Such advancements are pivotal in improving therapies for both solid and liquid tumours, including CAR T-cell and BsAbs treatments.

Bispecific Antibody therapy

Overview and Development

BsAbs represent a significant advancement in cancer therapy. Their dual targeting ability enhances tumour treatment effectiveness. BsAbs exist in various formats such as quadroma, F(ab')2, diabodies, tandem diabodies, and single-chain variable fragments (scFv), detailed in Figure 3. Previously, antibody engineering faced challenges, leading to the development of the Knobs-into-Holes heterodimerization technique for CH3 domains by Carter and colleagues at Genentech in 2016. This method, while innovative, encountered issues like shared light chain usage and glycosylation problems. Advanced recombinant DNA technologies subsequently addressed these challenges, facilitating the production of diverse antibody forms including single-chain tandem Fv bispecific and scFv. According to [79], these forms enhance binding characteristics, improving specificity and affinity, and broadening application scope.

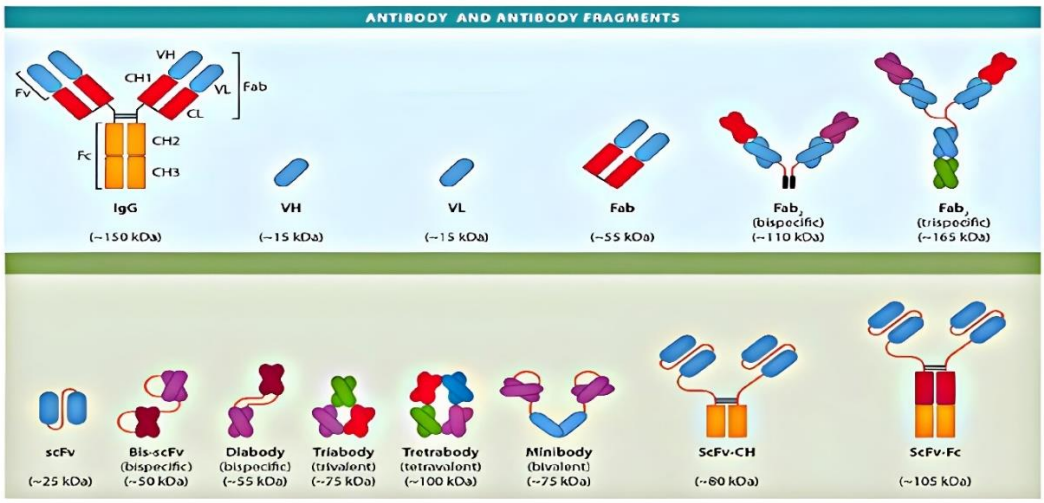


Figure (3): illustrates a conventional antibody, Immunoglobulin G (IgG), and its genetically modified variants (P M Lopez et al.,Cancers 2022,14[17])[80].

IgG, the most common antibody in human serum, has four subclasses [IgG1-4). Its structure, comprising two light and two heavy chains, forms a Y-shaped configuration. This arrangement includes three protein segments connected by a hinge region [81], each segment showing symmetry with two fragment antigen-binding (Fab) regions and one fragment crystallizable (Fc) region [82]. The Fab domain, containing hypervariable regions from heavy and light chains, mediates antigen binding [83]. Understanding antibody architecture and isotypes is vital for bispecific antibody design. Figure 4 showcases antibody isotypes such as IgA, IgG, IgM, IgD, and IgE. Bispecific antibodies are categorized into non-IgG-like, lacking Fc fragments, and IgG-like, incorporating Fc fragments [84].

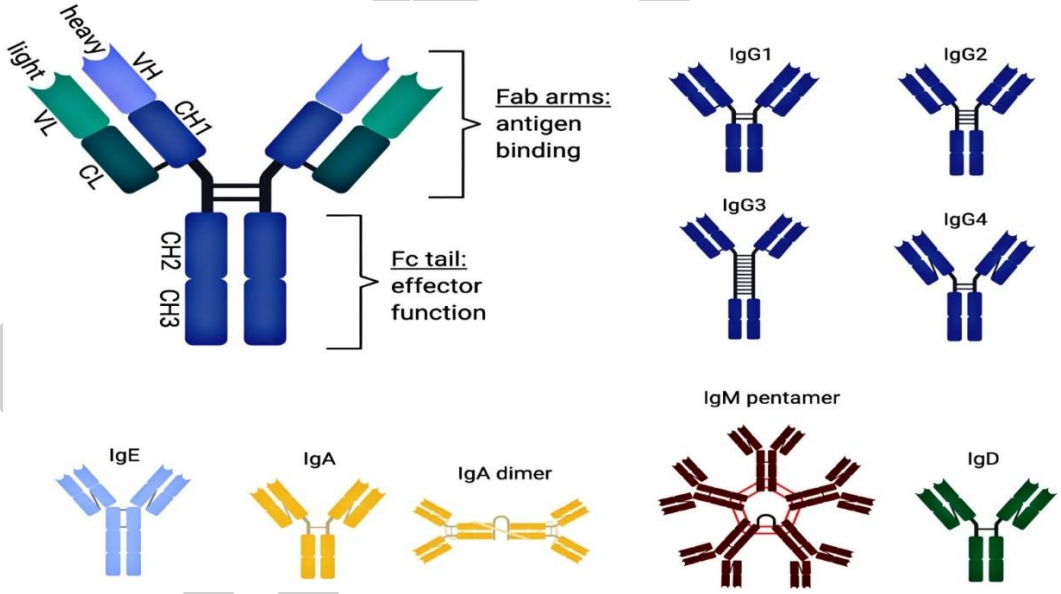


Figure (4): Human antibodies are categorized into five primary isotypes: IgG, IgA, IgM, IgE, and IgD. These isotypes are further divided into subclasses. Despite their diversity, all isotypes share a common structural layout. This layout includes two heavy and two light chains, which are connected by disulphide bonds. The chains comprise a variable domain (VH and VL) and constant domains (CH1, CH2, CH3, and CL). Antibodies function through two subunits: The Fab, which is responsible for specific antigen binding, and the Fc, which activates effector functions (Vukovic N et al., Clinical and Experimental Immunology 2020,203[3])[85].

The concept of BsAbs has evolved over more than five decades, with origins tracing back to the pioneering work of Nisonoff and colleagues [86]. These early researchers provided insights into antibody architecture. Unlike natural antibodies, BsAbs are primarily created using techniques such as recombinant DNA or cell-fusion technology. Initially, their design aimed at applications like redirecting T cells towards cancer targets. They were also used for binding simultaneously to tumour cells and an activating Fcγ receptor. The production methods of BsAbs have seen significant evolution. In their early stages, BsAbs were created using methods like manipulating monoclonal antibody hinge cysteines and through hybridoma fusion. A transformative shift in BsAbs production occurred with the advent of recombinant DNA technology [86]. This technology marked a new era in BsAbs development. Although the concept of BsAbs emerged in the 1960s, it wasn't until the 1980s that the first monoclonal BsAbs were successfully developed [87]. The early 1990s witnessed the documentation of their therapeutic applications. Over the last decade, there has been a surge in publications dedicated to BsAbs, indicating growing interest in

their therapeutic potential [87]. This increased interest in BsAbs has led to significant milestones in their therapeutic application. In 2009, catumaxomab received approval for therapeutic use. It was followed by the approval of blinatumomab in 2014. These approvals were pivotal advancements in the field of bispecific antibody therapy, marking the beginning of a new chapter in medical treatment and research [87].

Mechanism of action

BsAbs are advanced therapeutic proteins used in cancer treatment. Their function hinges on connecting immune cells to cancer cells, thus triggering an immune response against the cancer [88]. BsAbs are uniquely designed with dual binding sites: one targets cancer-specific markers, and the other latches onto immune cells. This dual targeting is crucial for directing the immune attack on cancer cells [89]. The effectiveness of BsAbs lies in creating an 'immunological synapse,' a link between cancer and immune cells [90]. There are two types: bispecific T cell engagers (BiTes) and immune effector cell-engaging bispecific antibodies (ICEs). BiTes connect T cells to cancer cells, while ICEs target various immune cells, like T cells or NK cells, to destroy cancer cells effectively [91].

Function of BiTes and ICEs

BiTes consist of two specific parts: one binds to cancer markers, and the other to the CD3 complex on T cells. This configuration directs T cells to attack cancer cells. Similarly, ICEs are tailored to bind specific immune cells, facilitating a targeted attack on cancer cells (Figure 5).

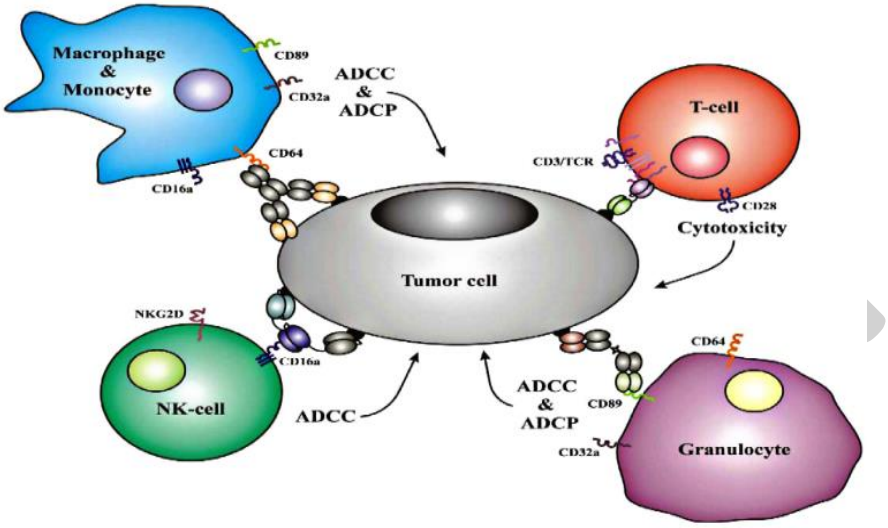


Figure (5): Tumour cell elimination involves using a therapeutic protein derived from antibodies to tag the cells. Effector cells are then recruited for the elimination process, which can occur through various mechanisms like ADCC, ADCP, or cytotoxic T-cell reactions. The agents involved include a monoclonal antibody, a chemically linked bispecific F(ab)2, and a recombinant bispecific tandem single-chain Fv-fragment (bsscFv) (Stein C et al., Antibodies1(1) 2012)[92].

BsAbs also interact with Fc receptors on immune cells and activate checkpoints like CTLA-4 and PD-1/PD-L1 (Figure 6). This interaction enhances the immune cells' ability to induce cancer cell death and inhibit tumour growth, underscoring the potential of BsAbs in cancer therapy [93-94].

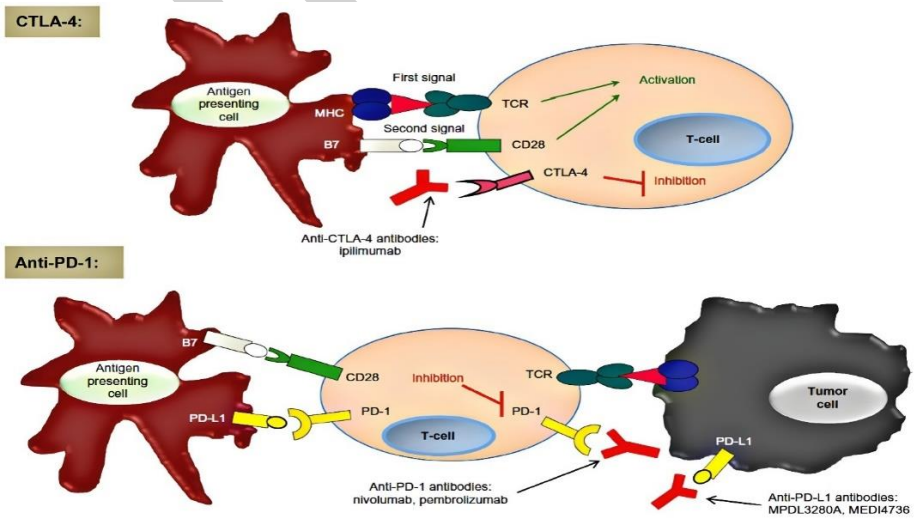


Figure (6): T-cell activation requires two signals. Post-activation, CTLA-4 can inhibit T-cell responses, but anti-CTLA-4 antibodies lift this inhibition, enhancing T-cell activity. Similarly, PD-1 on T-cells, when interacting with PD-L1 and PD-L2, generally suppresses their response. Anti-PD-1 antibodies help overcome this, boosting T-cell function in targeting cancer. This summary focuses on the roles of CTLA-4 and PD-1 in T-cell regulation, vital for understanding cancer immunotherapy (P Momtaz et al., Taylor& Francis 2014)[95].

Clinical applications

Bispecific antibodies (BsAbs) have significantly expanded the therapeutic landscape of cancer immunotherapy, demonstrating remarkable efficacy across various malignancies, including multiple myeloma [96]. Notably, blinatumomab has received FDA and EMA approval for treating refractory or relapsed pre-B cell acute lymphoblastic leukemia (pre-B-ALL) in both adults and children [97-101]. BsAbs also hold promise in targeting specific markers such as HER2 in breast and gastric cancers, PSMA in prostate cancer, and glypican 3 (GPC3) in liver, lung, and other cancers [102].

Immunotherapy has become a pivotal component in cancer treatment, alongside traditional modalities like surgery, radiation therapy, and chemotherapy, offering transformative potential [103]. Combining antibodies with adoptive cellular therapy and vaccination is gaining attention for its synergistic effects in cancer treatment [104-105]. BsAbs, with their ability to engage two distinct epitopes, are advancing cancer diagnostics and therapy, demonstrating enhanced efficacy and cost-effectiveness compared to using twoseparate monoclonal antibodies. This progress is exemplified by the FDA's approval of blinatumomab for B-cell precursor acute lymphoblastic leukemia and amivantamab for non-small cell lung cancer, reflecting the evolution of immunotherapy [106]. Addressing the challenge of treating lymphoid malignancies highlights the importance of integrating personalized therapy with bispecific antibodies and immune checkpoint inhibitors [107]. Particularly in lymphoid neoplasms, bispecific antibody immunotherapy stands out as a potent strategy [108]. Notably, bispecific antibodies with lower CD3 affinity have shown promise in eliminating tumour cells and reducing cytokine release syndrome (CRS) in prostate cancer, signifying significant progress [109]. In the context of glioblastoma multiforme (GBM), targeting EGFRvIII with T-bispecific antibodies is emerging as a promising approach. However, effective systemic delivery across the blood-brain barrier (BBB) remains a challenge [110-111].

Comparative analysis with other therapies

In the realm of bispecific antibody therapies, addressing challenges such as immunogenicity and endogenous biotin interference is crucial. One leading strategy is Pretargeted Radioimmunotherapy (PRIT) using nonimmunogenic human or humanized antibodies, which effectively reduces problems associated with immunogenicity and biotin interference. An example of this approach is the HER2 T-cell-dependent bispecific antibody (TDB), featuring low-affinity HER2 arms that improve tumour targeting and offer better tolerability compared to HER2-targeted CAR-T cell therapies, as supported by clinical data [112]. On the other hand, the SA-biotin method, while effective, faces significant immunogenicity issues due to streptavidin (SA). This pose concerns for repetitive use in therapy cycles. Strategies to mitigate this include developing genetically engineered SA variants with reduced immunogenicity and designing mutant SA molecules. These mutants bind less to endogenous biotin while maintaining high affinity for synthetic radio-biotin ligands, as explored in various studies.Furthermore, bispecific antibodies demonstrate superior selectivity and efficacy compared to monoclonal antibodies, particularly in treatments requiring high specificity like antibody-drug conjugates (ADC) and CAR T cell therapy. By targeting multiple antigens, they enhance effectiveness and minimize toxicity, a significant advantage highlighted in recent research [113].

Efficacy and Safety

Cancer immunotherapy, such as ipilimumab targeting CTLA-4, a protein that regulates immune responses, presents unique challenges compared to conventional treatments [114]. Despite the potential of BsAbs in cancer treatment, they can cause immune-related adverse events (irAEs), including elevated cytokine levels, which are overproductions of immune system proteins [87]. Strategies like premedication and gradual dose increases are proposed to manage these irAEs [115], offering insights into treating immune-mediated diseases [116]. New BsAbs, notably AFM13 targeting CD30/CD16A, show promise in reducing irAEs [116]. This antibody connects to both cancer and immune cells, potentially enhancing cancer cell destruction. Combining T-bispecific antibodies with anti-PD1 monoclonal antibodies—immunotherapies that block PD-1 proteins on T-cells to strengthen immune responses—has shown increased T-cell activity in preclinical studies [117-118], indicating a robust approach in cancer therapy [10]. In a study involving PF-06863135 (PF-3135), a bispecific humanized monoclonal antibody, results from 23 patients indicated one complete response, two minimal responses, and nine cases of stable disease, mostly with manageable side effects. However, six patients experienced grade 3 CRS [119].

Blinatumomab, evaluated in three studies for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), a type of lymphatic system cancer, showed specific dosing and response effectiveness [120]. Likewise, REGN5458, a bispecific antibody, displayed potential in treating multiple myeloma, a white blood cell cancer, in preclinical studies [121]. Catumaxomab has been effective against malignant ascites in epithelial cancers. Duligotuzumab, or MEHD7945A, demonstrated encouraging outcomes in treating head and neck squamous cell carcinoma, with a different side effect profile compared to cetuximab [122]. Additionally, combining blinatumomab with a tyrosine kinase inhibitor, a medication blocking enzymes in cancer cells, showed effectiveness in certain leukemia cases [123]. Lastly, FBTA05 showed positive responses in paediatric recurrent or refractory B-cell malignancies, types of cancer affecting specific white blood cells, with documented side effects [124].

Adverse effects

Common Adverse Events (AEs) of Bispecific Antibodies: This study highlights several side effects common in bispecific antibody therapy, a cancer treatment method. Patients often experience lymphopenia, pyrexia, elevated C-reactive protein, fatigue, leukopenia, weight gain, and headaches. Notably, transient blood disorders are common, with febrile neutropenia occurring in 3% of patients [125].

Cytokine Release Syndrome (CRS): A notable adverse effect of T-cell-engaging immunotherapies, including bispecific antibodies and chimeric antigen receptor T-cell therapies, is CRS. This condition, marked by a systemic inflammatory response, can be triggered by infections, drugs, or biological therapies, and manifests in symptoms like fever, nausea, and fatigue [126].

Hematologic Abnormalities: The report emphasizes the importance of monitoring blood-related abnormalities in patients undergoing bispecific antibody treatment. These include thrombocytopenia, lymphopenia, anaemia, and neutropenia, crucial for managing the safety of patients with both solid and liquid tumours [125].

Future directions

BsAbs, particularly effective in treating hematologic malignancies due to their clinical efficacy and manageable toxicity, are facing challenges that require addressing [108]. To optimize their use, there is a need for simplifying BsAbs structures, streamlining production, selecting synergistic target pairs, engineering non-immunogenic BsAbs, and developing strategies to minimize adverse effects. Notably, the potential of BsAbs extends beyond hematologic malignancies, with ongoing research exploring their applications in solid tumours [108]. The insights gained from their use in hematologic malignancies are anticipated to enhance treatments for solid tumour patients. A significant trend in the field is the rapid expansion of BsAbs in the pipeline, with many expected to enter the market in the next 3-5 years [113]. This marks a period of accelerated advancement, poised to transform cancer therapy. Furthermore, the field is evolving towards the development of multispecific antibodies, such as trispecific and tetraspecific antibodies, derived from BsAbs. These innovative antibodies offer enhanced selectivity and efficacy, presenting a promising direction for cancer treatment [113]. In the realm of next-generation cancer therapies, bispecific antibodies stand out, offering new, more effective, and targeted treatment strategies [127]. The continuous research and development of BsAbs are crucial for improving outcomes in both hematologic malignancies and solid tumours [127].

Combination therapies

The Hyper-CVAD chemotherapy regimen, comprising Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone, is a cornerstone treatment for newly diagnosed B-cell acute lymphoblastic leukemia (B-ALL) patients [128]. An innovative approach being explored is the combination of Hyper-CVAD with blinatumomab in a phase 2 study for newly diagnosed adult B-ALL patients [129]. This protocol involves four cycles of Hyper-CVAD followed by four cycles of blinatumomab, representing a strategic effort to enhance B-ALL treatment outcomes. This combination leverages Hyper-CVAD's established efficacy and blinatumomab's novel therapeutic potential, underscoring the commitment to advancing treatment options for B-ALL patients [129].

Comparative Analysis

Liquid tumours

CAR T cell therapy has significantly advanced the treatment of hematologic malignancies, especially B cell neoplasms like diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma [130]. These therapies are crucial for cases resistant to or relapsed after standard treatments, including immunochemotherapeutic and transplantation. For instance, CTL019, targeting CD19 in B-cell cancers, achieves high response rates and durable remissions, boosting immune recovery in many patients. However, about 33% of patients experience transient encephalopathy and 20% face severe cytokine-release syndrome [40]. This data, from a study backed by Novartis (ClinicalTrials.gov number, NCT02030834), underlines the efficacy of this therapy in certain hematologic malignancies. In DLBCL, the therapy response rate is 66%, with a 3-year event-free survival rate of about 20% post-rituximab autologous stem-cell transplant. Follicular lymphoma shows a 20% early relapse rate post-rituximab treatment, with a 50% 5-year survival rate. In refractory or relapsed cases, treatments like idelalisib or copanlisib yield median response durations of 10.8 and 12.2 months, respectively [131-132]. CD19-targeted CAR T cells are particularly promising for B-cell cancers [133-136].

CAR T-cell therapy's side effects, including cytokine-release syndrome and neurotoxicity, are notable [40]. Severe cytokine-release syndrome can be managed with tocilizumab [135]. Neurological effects range from mild disturbances to severe encephalopathy. Patients with progressive or unresponsive DLBCL or those relapsing post-transplantation, have a response rate of 20-30% and a median survival of about 6 months [137]. Refractory follicular lymphoma patients treated with idelalisib post-rituximab have a 22% 2-year survival rate [131]. BsAbs like Blinatumomab, are effective in Relapsed/Refractory Multiple Myeloma (RRMM) and B-cell precursor ALL, achieving a 32% complete remission rate in adult ALL treatment [138] and showing promise in minimal residual disease [139]. Daratumumab, another BsAbs, demonstrates anti-myeloma activity with minimal cytokine release [140], though concerns about toxicity remain. BsAbs can be used immediately, unlike CAR T cell therapy, but may be less effective due to the lack of T-cell co-stimulation [97, 141-142]. CAR T cell therapy's Overall Response Rates (ORR) are higher than BsAbs in RRMM and B-ALL [143-146]. Blinatumomab retreatment in B-ALL has a 36% ORR, with ongoing trials examining CAR T cell retreatment feasibility [147]. Current research is exploring BsAbs in early-stage Multiple Myeloma therapy and combating drug resistance, with clinical trials investigating combinations of various immunotherapies.

Solid tumours

Blinatumomab (CD3xCD19), a BsAbs approved by the FDA, effectively treats haematological cancers, especially B-cell malignancies. It achieves over 40% in complete or partial responses, enhancing survival rates in these diseases [97, 148-149]. Flotetuzumab (CD3xCD123 BsAbs) shows a 30% response rate in acute myeloid leukemia [150], while epcoritamab (CD3xCD20 BsAbs) demonstrates high efficacy in early studies, with a 44% complete response in DLBCL or HGBCL and 100% partial response in FL patients [151-153]. However, CD3-BsAbs show limited effectiveness in solid tumours, underscoring the need for more research, particularly in comparing their efficacy to CAR T-cell therapies in these tumours [154].

In ovarian cancer, CAR T-cell therapies targeting antigens like TAG72, MUC16, Her2, Meso, 5T4, and FRα have shown promise. TAG72-specific CAR T cells reduce tumour growth and enhance survival in preclinical mouse models [155]. MUC16-CAR T cells achieve complete regression of ovarian cancer in these models. Additionally, CAR T cells targeting Her2, Meso [156], 5T4 [46], and FRα [157] effectively inhibit ovarian cancer cell growth [154]. In breast cancer, HRG1β-based CAR T cells target HER family receptors to combat resistance [158], and human anti-HER2 CAR T cells destroy HER2-overexpressing cells [159]. Mesothelin-targeting CAR T cells are also being developed for breast cancer. In prostate cancer, PSMA-targeted CAR T cells show significant cytotoxicity [160], with clinical trials confirming their safety and efficacy in advanced cases [161]. Renal cell carcinoma treatments include CAR T cells targeting CA-IX [162-163], effective under hypoxic conditions [164]. In gastric cancer, bi-specific Trop2/PD-L1 CAR T cells exhibit strong efficacy [165], with ongoing research into CAR T cells targeting Claudin18.2, NKG2D, FOLR1, HER2, and ICAM-1 [166-170]. CAR T cells also show potential in pancreatic [171] and liver cancers, targeting antigens like CEA, glypican-3,

mucin-1, and carcinoembryonic antigen [172-173]. However, treating solid tumours with CAR T cell therapy is challenging compared to blood cancers. Solid tumours, often confined to a single organ, have diverse and evolving antigens and are surrounded by immunosuppressive environments that hinder CAR T cell migration, unlike blood cancers [174].

The amalgamation of CAR T cell therapy with additional therapeutic modalities

The integration of CAR T cell therapy with additional treatments represents a promising strategy for enhancing its efficacy against tumours. This novel approach combines CAR T cells with supplementary therapeutics, particularly beneficial in addressing solid tumours [174]. Incorporating CAR T cells with existing drugs opens new therapeutic avenues. Current clinical treatments often do not include adoptive cell therapy (ACT), but combining these methods necessitates understanding drug-immune system interactions. A notable example is lenalidomide, which has shown significant antitumor effects in multiple myeloma. When used in conjunction with CAR T cells, lenalidomide amplifies T cell infiltration and boosts IFNγ production and cytotoxicity. This synergy led to complete remission in treated mice, highlighting the potential of this combined therapy for managing solid tumours.

Overcoming physical barriers to achieve tumour localization

CAR T cells, a type of cancer therapy, face two main challenges in treating solid tumours. First, they must penetrate the tumour's dense structure, primarily made of fibroblasts and myeloid cells. These cells create a fibrous network called the extracellular matrix (ECM), which acts as a barrier. Wang et al. developed FAP-CAR T cells, which target and reduce fibroblasts, easing the way into the tumour and slowing its growth. Second, once inside, CAR T cells encounter the tumour microenvironment (TME), a space that suppresses the immune system. This environment contains elements like regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumour-associated macrophages (TAMs), along with factors like TGF-β and IL-10 that weaken the immune response. Checkpoint inhibitors such as PD-L1 also contribute to this suppression. To counter this, researchers like Caruana et al. have modified CAR T cells to express heparinase (HPSE), an enzyme that breaks down the ECM, facilitating easier T cell infiltration.

The immune-constraining environment within the tumour

Enhancing CAR T cell therapy involves not just getting these cells into the tumour but also ensuring they work effectively once there. Strategies include local antibody secretion to attract different immune cells into the TME [174], and using specialized CAR T cells like EGFRvIII CAR T cells. These cells target a specific protein on tumour cells, offering a focused approach with fewer side effects. Tuned CARs are another innovation, designed to identify and attack less common tumour antigens effectively. Additionally, 'iCARs' specifically target tumour cells, minimizing the impact on healthy cells, and include 'suicide genes' to eliminate the CAR T cells if necessary. Overall, these advancements in CAR T cell therapy highlight a multi-faceted approach to overcome the physical and immunosuppressive barriers presented by solid tumours.

Challenges and considerations

Immunogenicity of CAR T Cells

A major hurdle in CAR T cell therapy is its immunogenicity, specifically due to the CAR constructs [175]. These constructs often include non-human elements that trigger immune responses, leading to early clearance of the infused cells. Studies, including those referenced by [176], have provided strong evidence of such immune responses [175].

Antigen Escape in CAR T Therapy

Additionally, antigen escape poses a significant challenge, as demonstrated in studies at the University of Pennsylvania and the National Cancer Institute (NCI). This phenomenon, particularly in CD19-CAR therapy, is a leading cause of relapse. Similar issues of antigen loss have been documented in CAR therapies targeting multiple myeloma and glioblastoma [177].

Immunogenicity Risk in Bispecific Antibody Therapy

In the realm of bispecific antibody therapy, the risk of immunogenicity is a key concern. Certain antibodies, designed for simultaneous checkpoint inhibition and immune cell activation, present heightened immunogenicity risks. This is particularly evident in combination therapies that involve drugs like nivolumab (anti-PD-1 mAb) and ipilimumab (anti-CTLA-4 mAb), known for their increased antibody-related immunogenicity [178].

Bispecific Antibodies and Tumour Cell Immune Evasion

Recent studies show that certain bispecific antibodies, though effective in activating T cells, may inadvertently encourage tumour cells to adopt immunosuppressive tactics. Such adaptation allows these cells to avoid destruction by antibody actions, posing a significant challenge in effective cancer therapy.

Cost Considerations and Accessibility

The implementation of CAR T cell and bispecific antibody therapies, although promising, is fraught with challenges, primarily due to their complexity and the high incidence of AEs. These therapies are currently limited to specialized tertiary centres equipped for intensive care and monitoring [179], restricting access for many patients. Efforts are underway to facilitate outpatient administration, which could increase accessibility. However, the prevalence of early-onset toxicities remains a significant obstacle to this transition [179].

Financially, these therapies impose a heavy burden on patients and their families due to the prolonged nature of the toxicities and the need for specialized care. It's imperative to have transparent discussions about the financial implications before starting treatment. The lack of global guidelines for evaluating and managing toxicities related to CAR T cell therapy and bispecific antibodies further complicates the situation [179].

These innovative treatments hold great potential in cancer therapy, yet their accessibility is a pressing societal concern. It raises important questions in political discourse about whether such life-saving treatments should be a privilege of the wealthy or a right for all in need [180].

Manufacturing Complexities

The manufacturing process of CAR T cell therapies, typically conducted in distant facilities, adds to the challenges. It involves time, cost, and logistical complexities. Improving this process is essential to extend access to patients, especially those with rapidly progressing diseases, living far from manufacturing sites, or in resource-limited settings [180]. A promising alternative is innovating CAR T cell production to an in vivo approach, where a T cell-targeted transgene and transfer vehicle are introduced directly into the patient. However, this method faces significant technical, safety, and control challenges [180].

Manufacturing BsAbs also requires substantial investment in time and finances. It involves establishing secure and efficient cell lines, meticulous processing, and precise analytical purification methods [12]. Post-production, BsAbs face issues like degradation, aggregation, denaturation, fragmentation, and oxidation. Addressing these challenges is crucial for patients to fully benefit from these advanced therapies [12].

Conclusion

The fusion of CAR T cell and BsAbs therapies is revolutionizing cancer treatment. CAR T cells excel in treating blood cancers but face challenges in solid tumours. Enhancements are needed for wider applicability and is also being explored for the treatment of various pathological conditions such as autoimmune diseases, fibrotic diseases, infectious diseases, etc. Bispecific antibodies bridge immune cells and tumour cells effectively in both blood and solid cancers. This versatility holds promise for more effective treatments. Emerging trends focus on improving CAR T cell therapy through diverse molecular mechanisms and optimizing Bispecific antibody therapy. The rise of multispecific antibodies and advancements in BsAb technology herald a new era of targeted cancer treatments. These immunotherapies are converging to offer personalized treatment options. Ongoing research aims to unlock their full potential against the varied challenges of solid and liquid cancers.

Ethics approval and consent to participate

This manuscript is a review study. Hence, ethics approval and consent to participate are not applicable.

Consent for publication

Not applicable

Availability of data and materials

All data related to this study is included in the manuscript.

Authors contribution

Saritha Medapati: Conceptualization, data curation, validation, visualization, reviewing and editing and supervision. **Haripriya B.V.S.L:** Conceptualization, writing of original draft, data curation and editing. **Priyanka Jyothi Dummari:** conceptualization, writing of original draft, data curation, writing review and editing. **Vinodkumar Mugada:** Data curation, visualization, software, review and editing. **Rooth Vasantha Medapati:** data curation, visualization, validation, writing review and editing. **Srinivas RaoYarguntla:** supervision, administration, resources.

Competing interest

None.

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