OPINION

SHIFTING GEARS:

CAR NK-CELL THERAPY VS. CAR T-CELL THERAPY

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Chimeric Antigen Receptors (CARs) are engineered receptor proteins that target specific antigens on the surface of cancer cells. CAR-based therapies have emerged as promising avenues in oncology.[1] Among these, the most extensively studied and applied treatment is CAR T-cell therapy, which involves harvesting a patient's T cells and genetically modifying them to express CARs.[2] However, recent studies have demonstrated that Natural Killer (NK) cells may be a more effective foundation for CAR-based therapies, considering their innate killing ability, potential for over-the-counter accessibility, and increased safety profile.[1]

CAR T-CELL THERAPY: CURRENT APPROACHES AND LIMITATIONS

CAR-based therapies reprogram immune cells, such as T cells, to recognize and eliminate malignancies with high specificity by selectively binding to cancer-specific antigens. This process involves separating immune cells from the blood of the patient (autologous therapy) or a healthy donor (allogenic therapy). Viral vectors and CRISPR-Cas9 can then be used to insert synthetic DNA sequences encoding CARs into immune cells, allowing them to express chimeric receptors with the desired antigen-binding domains.[1,2] Thus, compared to conventional, broadly-acting cancer treatments such as chemotherapy and radiation, CAR T-cell therapy minimizes collateral damage to healthy cells. An additional advantage is the ability of engineered T cells to persist in the bloodstream for extended periods of time, providing long-term surveillance against cancer recurrence.[3] Over the years, CAR T-cell therapy has demonstrated notable efficacy in various hematological tumours, including multiple myeloma, leukemia, and lymphomas.[2]

However, CAR T-cell therapy is associated with several drawbacks. For instance, it may induce antigen escape, where tumours evade immune response by reducing the expression of targeted antigens.[5] Another difficulty is the identification of tumour-specific antigens (TSAs) which are scarcely expressed.[6,7] Therefore, tumour-associated antigens (TAAs), which are expressed on normal cells and abnormally in tumour cells, are more commonly used in CAR T-cell therapy. However, TAAs can induce side effects, specifically in cases of solid tumours, where healthy cells expressing the same TAAs become targeted. Additionally, due to physiological barriers of the immunosuppressive tumour microenvironment (TME), as well as antigen heterogeneity and tumour stroma, CAR T-cell therapy is less effective against solid tumours compared to hematological malignancies.[8]

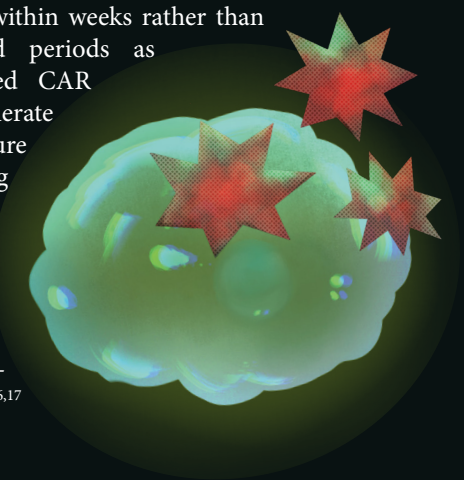
Furthermore, excessive activation of CAR T-cells can trigger toxicities such as cytokine release syndrome (CRS), a potentially life-threatening inflammatory response characterized by fever, headaches, nausea, hypotension, and multi-organ dysfunction.[2,6] Conversely, inadequate persistence of CAR T-cells has led to cases of disease relapse. Additionally, T cell exhaustion can lead to insufficient expansion or premature loss of CAR T-cell activity.[4] Tonic signaling-induced exhaustion, a type of T cell exhaustion, can result in upregulation of inhibitory receptors, impaired proliferation, and activation-induced cell death that compromises therapeutic efficacy.[16] Finally, CAR T-cells can trigger severe inflammatory responses like graft-versus-host disease (GvHD) in allogeneic settings, where donor CAR T-cells recognize the patient's cells as foreign and attack them.[5]

THE POTENTIAL OF NK CELLS

CAR NK-cell therapy targets cancer cells with high specificity and has distinct safety advantages over CAR T-cell therapy, due to their limited in-vivo persistence and reduced risk of CRS. Additionally, CAR NK-cells demonstrate inherent tumour-killing capabilities with minimal off-target toxicity.[2]

CAR T- and CAR NK-cells both have multiple recognition pathways and killing mechanisms, including perforin and granzyme release and death receptor activation, which act as safety mechanisms to help prevent tumour escape. However, the cytotoxic activity of CAR NK-cell can act non-specifically, while CAR T-cells require the recognition of antigens. CAR NK-cells also express receptors required to activate antibody-dependent cell-mediated cytotoxicity (ADCC). Unlike T cells which rely on antigen recognition through the T cell receptor (TCR) complex, NK cells express a number of germline-encoded activating and inhibitory receptors. These receptors allow NK cells to recognize antigen-independent stress signals and altered self-markers on malignant cells.[2] Furthermore, NK cells have a unique relationship with major histocompatibility complex (MHC) molecules, which are generally downregulated in cancer cells to avoid detection by cytotoxic T cells. This absence of MHC I triggers the activation of NK cells rather than inhibition, creating an additional layer of specificity.[9]

CAR NK-cell therapy is also less toxic than CAR T-cell therapy because of several biological characteristics. For example, NK cells do not produce pro-inflammatory cytokines associated with CRS in CAR T-cell therapy.[9] This signature cytokine profile significantly reduces the risks of toxicity and CRS adverse events. Additionally, a common life-threatening complication of CAR T-cell therapy called immune effector cell-associated neurotoxicity syndrome (ICANS) has not been observed with CAR NK-cell therapy in clinical studies.[10] Furthermore, the shorter lifespan of NK cells provides a built-in safety mechanism, as any unexpected toxicities would resolve naturally within weeks rather than persisting for extended periods as observed with long-lived CAR T-cells.[11] CAR NK-cells tolerate sustained cytokine exposure without experiencing toxicities, as they depend on cytokines for survival, compared to CAR T-cells which demonstrate susceptibility to tonic signaling-induced exhaustion.[16,17]



The reduced risk of side effects of CAR NK-cell therapy enables outpatient administration.[2]

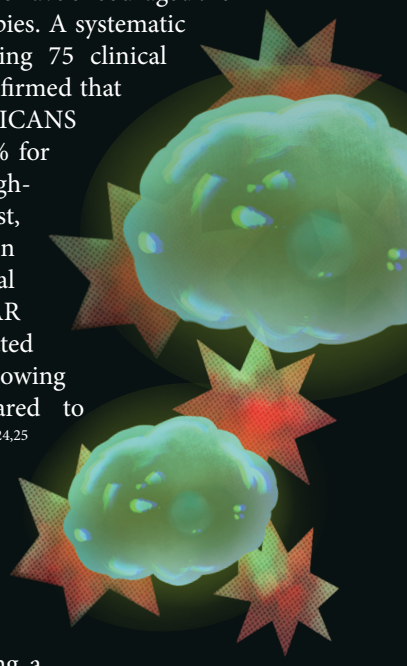
From an implementation perspective, CAR NK-cell therapy addresses several limitations associated with CAR T-cell therapies. Most approved CAR T-cell therapies are autologous to avoid the risk of GvHD with allogeneic transplant.[1] Non-specific allogeneic sources largely avoid GvHD concerns while significantly streamlining the production process for CAR NK-cells to generate readily available, "off-the-shelf" products.[1,12] The shorter production time is particularly crucial for patients with rapidly progressing diseases, where the weeks required for autologous CAR T-cell production can be clinically significant.

CAR NK-cell therapy's greatest advantage is its potential to target solid tumours. While CAR T-cell therapy has limited efficacy in solid tumours due to impaired tumour trafficking and infiltration, T cell exhaustion within the immunosuppressive TME, and reduced persistence at tumour sites, CAR NK-cells may overcome these barriers through their distinct biological characteristics.[18] NK cells can simultaneously target multiple tumour antigens through both CAR-dependent and independent mechanisms, providing a stronger response to tumour heterogeneity.[13] Recent innovations such as engineering NK cells with modified receptors have demonstrated the ability to overcome the immunosuppressive TME.[14] Other advances now allow co-expression of cytokines, antibodies, and proteases with CARs, enhancing NK cell tumour infiltration, outcomes that remain more challenging to achieve in CAR T-cell therapies.[1] This is because CAR T-cells engineered to secrete cytokines risk triggering severe CRS and neurotoxicity, with clinical studies reporting dose-limiting toxicity in a significant proportion of patients.[15]

The safety, efficacy, and manufacturing advantages favours CAR NK-cell therapy over CAR T-cell therapy. The economic implications of off-the-shelf production represent a paradigm shift in cellular therapy accessibility. The ability to manufacture CAR NK-cells as universal, allogeneic products eliminates the time-intensive process of individualized CAR T-cell production, which typically requires specialized manufacturing facilities, extensive quality control procedures, and costs exceeding $400,000 per patient.[19] The capacity to generate cryopreserved CAR NK-cell products from renewable sources further reduces production costs while ensuring immediate availability for patients, expanding access to cellular immunotherapy beyond specialized centers.[20] Thus, the integration of multiple targeting mechanisms, tolerance to sustained activation without exhaustion, minimal alloreactivity enabling universal donor compatibility, and safety features collectively establish CAR NK-cells as a potentially superior platform for both current applications and future therapeutic innovations in oncology.

CURRENT EVIDENCE OF CAR-ENGINEERED APPROACHES

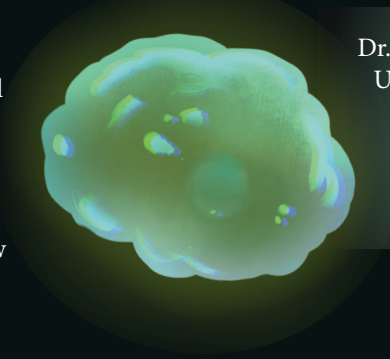
CAR NK-cell therapy offers substantial advantages over CAR T-cell therapy across multiple critical dimensions: safety profile, manufacturing, and therapeutic versatility.[21] The evidence synthesized throughout this review reveals that CAR T-cell therapy has achieved success in treating hematological malignancies.[22] However, the inherent biological limitations of T-cell-based approaches have encouraged the exploration of alternative cell therapies. A systematic review and meta-analysis examining 75 clinical trials comprising 3,184 patients confirmed that the overall pooled incidence rate of ICANS with CAR T-cell therapy was 26.9% for all-grade events and 10.5% for high-grade events.[23] In stark contrast, ICANS has not been observed in any CAR NK-cell therapy clinical trials to date.[24] Furthermore, CAR NK-cell therapies have demonstrated significantly lower CRS rates, showing a superior safety profile compared to autologous CAR T-cell therapies.[24,25]



FUTURE DIRECTIONS

As of October 2024, at least 120 clinical trials focused on CAR NK-cell therapy have been registered worldwide, with 32 initiated in 2024 alone, representing a marked acceleration in clinical development.[26] In the landmark phase 1/2 trial evaluating cord blood-derived CD19-directed CAR NK-cells treated with IL-15, the therapy demonstrated a 1-year overall survival rate of 68% and progression-free survival of 32% in heavily pretreated patients with CD19+ hematologic malignancies, with no patients developing GvHD or ICANS.

Several critical limitations and knowledge gaps must be acknowledged. First, the long-term efficacy of CAR NK-cell therapy remains uncharacterized. While the shorter lifespan of NK cells provides a built-in temporal limitation to potential toxicities, it raises concerns if the reduced persistence will translate to increased relapse rates.[28] NK cells typically exhibit limited in vivo persistence lasting only weeks to months without cytokine support, a natural characteristic that distinguishes them from the prolonged persistence observed with CAR T-cells, which can remain detectable for years.[27] Additionally, the manufacturing and expansion challenges with NK cells warrant consideration. Primary NK sources present technical obstacles as NK cells comprise only 10-15% of peripheral blood lymphocytes and demonstrate restricted ex vivo expansion capacity, making the production of sufficient doses challenging.[29] Moreover, the efficacy of CAR NK-cells against solid tumours, while theoretically promising, has yet to be definitively established in large-scale clinical trials; the majority of published CAR NK-cell data derives from hematological malignancy studies.[26]



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