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The Challenges and Future of CAR T-Cells for Treating Multiple Myeloma

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ABSTRACT

CAR T-cell therapy is a concept that modifies blood cells to fight against cancers. Studies have found that this hasn't had long-term effects, and research has been conducted to find challenges that could cause this. Multiple different antigens are one of these challenges, as well as inefficiency in this method of therapy are challenge to this concept. There are many advancements that have been made that help resolve some of these challenges. Different generations of these CARs allow for stronger cells. These generations are different layers of protection that involve modifications to make the CARs more efficient. Dual antigen specifically allows one CAR to target two different antigens, which could be present in the separate cells of the same cancer. NK-cell therapy is a different concept following the ideas of CAR T-cell therapy that could grow widely in the near future. This involves natural killer cells which are cells that are already programmed to kill these cells, making it unnecessary to modify them. This would also be much more efficient and has a lot of potential to become a commonly used treatment. These ideas were gathered through an in-depth exploration of CAR T-cell therapy for multiple myeloma discussing the current challenges and potential solutions within the field.

Introduction

For years, cancer has been a disease most commonly treated by surgery, radiotherapy, and chemotherapy. With these treatments, cancer has remained the second most common cause of death in the world. With more diagnosis, finding a cure or more treatments for cancer have become much more of a priority. Multiple myeloma (MM) is known as the cancer of white blood cells, or plasma cells, which are the cells that produce antibodies. This cancer is believed to start in long-lived plasma cells, which are plasma cells that form and live in the soft bone marrow for several months to years. MM can sometimes be detected in blood tests or bone x-rays. However, in order for a diagnosis to be confirmed, a bone marrow biopsy is often performed. Serum or urine samples are analyzed by electrophoresis to determine the presence of M-proteins, which usually signify myeloma. The three main treatments that are currently most common are chemotherapy, Autologous Stem Cell Transplant (ASCT), and novel agents. Chemotherapy is usually followed by ASCT, which is known to improve the quality of life for patients as well as enhance progression-free survival (PFS). There can also be double ASCTs, which have been shown to be effective in patients who have not achieved good responses from the first ASCT. A method of therapy used for non-transplant candidates is novel agents. Novel agents are drugs or medications given to the patient to keep the cancer under control, but these may not significantly improve the outcome or lead to a cure. Another method of treatment is monoclonal antibody treatment, which may halt tumor growth by blocking specific growth factors or critical pathways in the tumor cell.

In recent years, immunotherapy has become a standard therapy for MM. A form of immunotherapy that is now being introduced is chimeric antigen receptor (CAR)-T cell therapy, which involves isolation and genetic modification of T lymphocytes from the patient's blood to fight the cancer. In 2017, the Food and Drug Administration (FDA) approved this treatment for multiple myeloma, making it a more recent blood cancer to be approved for this treatment. Although it has significantly improved outcomes for MM, about half of the

patients still do not benefit from this type of therapy. Because this is a new approach, especially within the field of multiple myeloma, there is very limited research on the challenges and the potential strategies to mitigate them to improve the efficacy of CAR-T cells in MM.

Types of CAR-T Cells

CAR-T cells are not completely new cells, but they are T cells that have the CAR alterations done to them in the lab. T cell receptors (TCR) are receptors that are capable of killing the cancer, which is vital to this treatment. B-cell receptors (BCR) are receptors that can identify specific antigens in cancer cells. This therapy involves the TCR to bind to BCRs, which then makes the T-cells more powerful due to the fact that they now also have the capabilities of BCRs. Different types of CARs can also be different generations, meaning they have different layers of protection, and each new generation climbs toward higher activation and longer retention of CAR-T cells.

The first ever CAR that was approved by the FDA was the Idecabtagene vicleucel (ide-cel), which was a generation two CAR. This was used for refractory or relapsed multiple myeloma, meaning it wasn't used as a first resort treatment. This CAR was evaluated closely in the KarMMa trial around 2021. In this trial, 128 patients above the age of 31 who relapsed from previous treatments were given Idecabtagene vicleucel (ide-cel). 73% of the cohort responded to this treatment, with an average stable period of 8.8 months. It was also found that higher concentrations of the ide-cel provided better results, with 82% response and 12.1 stable months. These cells were found in the blood even after 12 months, meaning they were strong and durable, but they also do not prevent the myeloma from reappearing or growing. However, 84% of the patients developed cytokine release syndrome (CRS) which is when the immune system is hyperactive and secretes cytokines such as IL-6 which when in excess can be toxic to the body. (Manier, 2022) The SRS can cause fever and nausea, which can last a couple of weeks.

The second generation CAR that is BCMA directed is Ciltacabtagene autoleucel (cilta-cel). This is a CAR that rather than a single binding domain, has two camelid VH binding domains meaning it has less immunogenicity and higher activity. (Davis et al., 2022) When this receptor was observed in a study called CARTITUDE, also around 2021, it was found to have much better results than the ide-cel trial. The treatment was given to 97 patients, and there was a response rate of 98%, and 60% had a progression-free survival (PFS) of 24 months. Although the long-term results were much better, about 94% of the patients developed CRS. Within this, two cases of neurocognitive disorders have been reported after cilta-cel and one after ide-cel all being grade three. Grade three and four CRS also included neutropenia, anemia, and thrombocytopenia. (Manier, 2022)

Possible Challenges in CAR-T Cell Therapy

While CAR-T cell therapy is an excellent and effective treatment, like all treatments, there are ways for this to go wrong. The body detects unusual or foreign substances, and the immune system attacks them as part of the human body's safety system. The immune system constantly elicits responses to these treatments, which end up turning into mechanisms of resistance. These mechanisms typically fall into either the antigen-dependent category or the T-cell driven category.

A current limitation to this type of immunotherapy is that different tumor cells might have different types of the target antigen, and the CAR-T cell might not latch on to all of the types of target antigens. In addition to this, some of the target antigens might not be displayed anymore due to the fact that CAR-T is a

second resort treatment and previous treatments could have caused the tumor to no longer display these antigens. CAR-T cells with dual antigen-specificity can help with this, as they can target two antigens at the same time. This way, if different tumor cells have different antigens, they can all be targeted by the same cell and if an antigen is not being displayed, the T-cell can still latch onto another antigen.

Another limitation comes in autologous CAR-T cells because of the amount of time it takes after the cells are removed to modify and put them back into the bloodstream. This process has three steps: leukapheresis, manufacturing, and quality control. For patients who cannot have bridging therapy, an option is Allogeneic CAR-T cells. These are comparable to autologous CAR-T cells as they are taken from donor blood or umbilical cord blood. If these cells are class II, this is still considered human blood, so these cells will not be completely foreign to the body and are not likely to get attacked by the immune system. However, class I expression will be considered as foreign and will be rejected by the patient's immune system (HvGR).

Ide-cel and clita-cel are typically scFv and are not fully composed from human sources. Ide-cel has components that come from mice, and clita-cel has components that come from llamas. When these cells are inserted into the body, they may be recognized as foreign substances. This often causes the body to attack these cells, leading to an ineffective treatment. This discovery is pushing scientists to work on a new CAR that is composed of more naturally humanlike with the hopes of reducing the risk of antibody development against the treatment.

In all current CAR-T cell treatments, the CAR is BCMA targeted due to the fact that all myeloma calls have this antigen. One of the main mechanisms of resistance is BCMA antigen escape. When the targeted treatment occurs, the cancer cell sometimes stops displaying the BCMA on its surface, making the treatment completely ineffective. Fortunately, this isn't something that happens often and is in fact very rare. This is because of how important the BCMA antigen is, and this is shown in the KarMMa trial, where this only occurred with one patient. There are also times when this occurs not as a mechanism of resistance but just as a mistake when the cancer is relapsing. Again, this is extremely rare.

BCMA can turn into a soluble BCMA (sBCMA) and be released into the bloodstream. When this happens, it is easier to track the progression of the cancer by measuring the concentration and quantity of the sBCMA. These sBCMAs draw the CAR-T cells away from the tumor cells in a process called BCMA shedding, thus reducing the amount of modified CAR-T cells that will reach the actual target cancer cells. Preventing BCMA from turning into sBCMA could increase the number of BCMAs on the myeloma cells, allowing the CAR-T cells more antigens to latch onto. There are certain medications that can prevent this, but studies are being conducted to determine the efficacy of these treatments.

The idea of CAR-T cell therapy revolves around the T cells, which undergo a natural cycle of being fatigued and worn over time. This aspect contributes to the effectiveness of this treatment which varies among individuals at different stages of multiple myeloma. A particular type of T cell, which is known as CD8+ T, or stem memory T cells, plays a crucial role in eliciting a superior response to the treatment. These cells are more prevalent in individuals in the early stages of multiple myeloma, whereas individuals who have more exhausted cells exhibit a less robust response.

Strategies for Response Enhancement

CAR-T cell therapy is a relatively new concept and therefore has much more research to be done. There is much room for modifications and different versions of this treatment to make it more efficient and beneficial for the patients. These limitations and mechanisms of resistance require scientists to do more research and work around them. No two cases can be the same, so having different forms of this therapy or multiple ways to administer this treatment can make the results more specific to each patient. The current CAR-T cells that have been discovered bring many risks, limiting them and the amount of research that can be done with them. However, a

continuous effort will allow for more enhancements and modifications that will help make this treatment overall a more useful and effective treatment.

The second and third generation CARs were meant to help the growth and survival of the CAR T-cells, but the conditions and environment of multiple myeloma can still be harmful to or impact the function of the CAR T-cells. Commuting cells can be used to reverse the purpose of inhibitory signals and turn them into activating signals. If endodomains and ectodomains of different IL-4s are fused together, they can turn the inhibitory signals into proliferation signals. For IL-6 CAR [50], the CAR can only neutralize IL-6. This is because CARs aren't designed to neutralize any cytokines, but some of their modifications match with IL-6 causing it to neutralize. These generations are also when costimulation was first introduced in immunotherapy. Costimulation involves a signaling pathway where costimulatory signals allow for the activation of CAR T cells, which is used more commonly now.

Armored CAR T-cells are fourth-generation CARs that have been developed very recently. This generation of CAR has proteins that help reduce immunosuppression. These cells known as T-cells Redirected towards Universal Cytokine Killing (TRUCK) incorporate genes that cause the cells to release cytokines that interfere with the immunosuppressive cytokines of the cancer cell. A cytokine that can be released is IL-12 which can stimulate T helper 1 (Th1) cells to release Interferon-g (IFN-g) which, in turn, causes cells to turn into immune-stimulating cells rather than immunosuppressive cells. (Hawkins, 2021) This advancement in CAR T-cell therapy could be greatly beneficial as it would cause the immune system to continue fighting and even replace dead immune cells as opposed to the immune system shutting down or fighting weakly. When this is done in vivo, it allows the host immune cells to develop a memory and fight the cancer again at a later time - thus minimizing tumor recurrence. This strategy has shown effectiveness both in vitro and in vivo. While the IL-12 cytokine is a great way to fight immunosuppression, it has been shown to be highly toxic, to the point where it has caused two deaths. (Hawkins, 2021) Another cytokine that works very similarly to IL-12 is IL-18 by enhancing the function of the CAR T-cell. IL-18 also stimulates natural killer cells allowing for a wider range of weapons against cancer. This also is not nearly as toxic as IL-12, making it an overall better option. (Senju et al, Int. J. Biol. Sci., 2018)

A form of a dual targeting antigen is an AND-gate, which is when the cell binds to two antigens simultaneously. This is a good approach to achieve tumor specificity through the recognition of two antigens neither of which are specific to the tumor. In order for this to work, two antigens are needed that don't activate T-cells individually but trigger a powerful anti-tumor response, making this very complicated. A possible approach to this is the use of a NOTCH synthetic receptor that identifies the first antigen, which then allows for the expression of the second antigen being targeted. Another possibility is combining the expression of two different antigens and using that.

Multiple myeloma causes immune cell dysfunction in order for the cancer cells to grow. One of the receptors that induces cell exhaustion in CD8+T cells is called TIGIT, and it has been found to be one of the strongest of these receptors. When these receptor pathways were blocked, the function of CAR-T cells increased greatly, but there still are other pathways that are affecting CAR-T cell function. CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/ CRISPR-associated protein 9) is a new technology that can significantly change this. CRISPR/Cas9 is a technology that genetically modifies cells in the body and is used for quite precise genetic engineering. The PD-1 checkpoint knockout has been shown to facilitate apoptosis of multiple myeloma cells. This has become a target for CRISPR, and tests have found it to be successful. The introduction of a lymphocyte activation gene (LAG3) and other various checkpoints did not yield the same positive results. This has also been tried with different checkpoints and was unsuccessful. However, it was determined that after this concept is studied more and better targets are identified, and the method of CRISPR/Cas9 can be a very beneficial modification to the CAR T-cell treatment.

Natural killer cells are cells that have the ability to rapidly produce anti-tumor responses, which is why they have been considered as an alternative treatment to T-cells in CAR T-cell therapy. They are more versatile

as they don't change when the target changes, and thus don't need to be modified specifically to each target. When they were engineered and tried on patients with relapsed myeloma, the CAR-NK cells were found to be effective. This form of CAR therapy is much more efficient and can lead to more success in CAR therapy.

Method

This review is a qualitative exploratory study. The majority of the data is obtained from previously published literature and case studies. This research explains why there haven't been many long-term results for this form of treatment. It is known that Multiple Myeloma has no cure, and this now further explains why there are so many challenges. The searches done on Google Scholar and NCBI included the terms "CAR-T cell" and "CAR-T cell therapy," as well as searches including the terms "multiple myeloma" and "immunotherapy." The data from different clinical trials and the information from different literature reviews were combined and analyzed from a connecting point of view, to then be reinterpreted and written in this paper.

Discussion

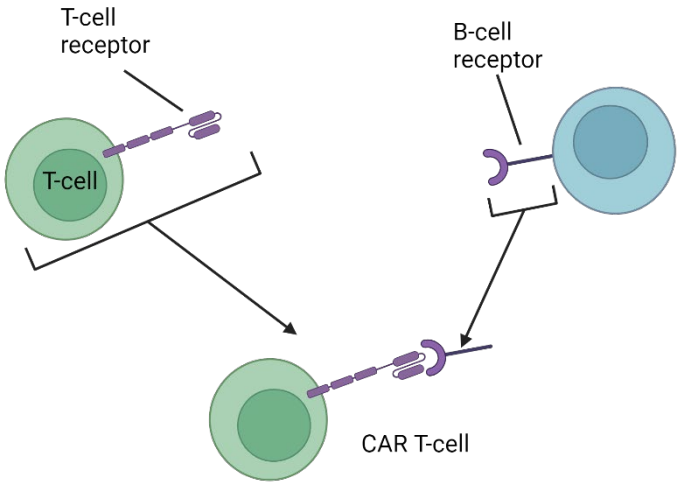

Figure 1. CAR binding to BCMA. All current CARs for multiple myeloma treatment are designed to bind to BCMAs which are a type of B-cell receptor. This is because this specific receptor is present on all multiple myeloma cells. The CAR is an attachment to the T-cell, so it binds to the receptor on its own. Created with BioRender.com

The current CAR-T cell therapy that is being used has had some limited success, but many factors have been found that reduce the efficiency of this process. New research is finding different ways to enhance this treatment and avoid or mitigate these previous challenges. These enhancements involve changing the targets and making

small adjustments that can completely change how these antigens work. This means that the previously mentioned below 50% success rate will no longer exist in the near future. While all the enhanced CAR therapies can be extremely beneficial in the realm of immunology, the NK cell therapy approach has the most potential to become common, especially due to the high amounts of research being done for it. This concept is being researched in many places all over the world. It is extremely efficient and effective, causing it to be more of a priority in research for immunotherapy. Although this approach is successful in MM, many challenges remain for it to be effective in solid tumors and may require a combination of CAR-T with other therapeutic approaches.

Table 1. Retrieved from NCBI (Pang et al.). Table representing different clinical trials nationwide studying NK cells and CAR NK cell therapy. It shows the different types of CAR-NK cells and the antigen that they are targeting

Clinical Trial	NK Source	Interventions	Conditions	Status	Locations	Phase
NCT04887012	U	Biological: anti-CD19 CAR-NK	B-cell Non Hodgkin Lymphoma	R	2nd Affiliated Hospital, School of Medicine, Zhejiang University Hangzhou, Zhejiang, China	Phase 1
NCT05213195	U	Drug: NKG2D CAR-NK	Refractory Metastatic Colorectal Cancer	R	The First Affiliated Hospital, Zhejiang University Hangzhou, Zhejiang, China	Phase 1
NCT05215015	U	Biological: Anti-CD33/CLL1 CAR-NK Cells	Acute Myeloid Leukemia	R	Wuxi People's Hospital Wuxi, Jiangsu, China	Early Phase 1
NCT04639739	U	Biological: anti-CD19 CAR NK	NHL	NY	Department of Hematology, Xinqiao Hospital ChongQing, Chongqing, China	Early Phase 1
NCT03692767	U	Biological: Anti-CD22 CAR NK Cells	Refractory B-Cell Lymphoma	UK		Early Phase 1
NCT03690310	U	Biological: Anti-CD19 CAR NK Cells	Refractory B-Cell Lymphoma	UK		Early Phase 1
NCT05008575	U	Biological: anti-CD33 CAR NK cells Drug: Fludarabine Drug: Cytoxan	Leukemia, Myeloid, Acute	R	Department of Hematology, Xinqiao Hospital Chongqing, Chongqing, China	Phase 1
NCT03692637	PB	Biological: anti-Mesothelin Car NK Cells	Epithelial Ovarian Cancer	UK		Early Phase 1
NCT03415100	PB	Biological: CAR-NK cells targeting NKG2D ligands	Solid Tumours	UK	Third Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China	Phase 1
NCT03692663	U	Biological: anti-PSMA CAR NK cells	Castration-resistant Prostate Cancer	UK		Early Phase 1
NCT05008536	U	Biological: Anti-BCMA CAR-NK Cells Drug: Fludarabine Drug: Cytoxan	Multiple Myeloma, Refractory	R	Department of Hematology, Xinqiao Hospital Chongqing, Chongqing, China	Early Phase 1

NCT03940820	U	Biological: ROBO1 CAR-NK cells	Solid Tumor	R	Radiation Therapy Department, Suzhou Cancer Center, Suzhou Hospital Affiliated to Nanjing Medical University Suzhou, Jiangsu, China	Phase 1 Phase 2
NCT03940833	U	Biological: BCMA CAR-NK 92 cells	Multiple Myeloma	R	Department of Hematology, Wuxi People's Hospital, Nanjing Medical University Wuxi, Jiangsu, China	Phase 1 Phase 2
NCT04847466	U	Drug: N-803 Drug: Pembrolizumab Biological: PD-L1 t-haNK	Gastroesophageal Junction (GEJ) Cancers Advanced HNSCC	R	National Institutes of Health Clinical Center Bethesda, MD, USA	Phase 2
NCT03824964	U	Biological: Anti-CD19/CD22 CAR NK Cells	Refractory B-Cell Lymphoma	UK		Early Phase 1
NCT05020678	PB	Biological: NKX019	Lymphoma, Non-Hodgkin B-cell Acute Lymphoblastic Leukemia Large B-cell Lymphoma (and 7 more)	R	Colorado Blood Cancer InstituteDenver, CO, USA University of Chicago Chicago, IL, USA The Cleveland Clinic Foundation Cleveland, OH, USA (and 4 more…)	Phase 1
NCT02944162	NK-92 cell line	Biological: anti-CD33 CAR-NK cells	Acute Myelogenous Leukemia Acute Myeloid Leukemia Acute Myeloid Leukemia With Maturation (and 2 more)	UK	PersonGen BioTherapeutics (Suzhou) Co., Ltd. Suzhou, Jiangsu, China	Phase 1 Phase 2
NCT03579927	umbilical Cord Blood	Procedure: Autologous Hematopoietic Stem Cell Transplantation Drug: Carmustine Drug: Cytarabine (and 5 more…)	CD19 Positive Mantle Cell Lymphoma Recurrent Diffuse Large B-Cell Lymphoma (and 4 more)	Withdrawn	M D Anderson Cancer Center Houston, TX, USA	Phase 1 Phase 2
NCT05182073	PB	Drug: FT576 Drug: Cyclophosphamide Drug: Fludarabine Drug: Daratumumab	Multiple Myeloma Myeloma	R	Colorado Blood Cancer Institute Denver, CO, USA Tennessee Oncology—Nashville Nashville, TN, USA	Phase 1
NCT05248048	U	Biological: CAR-T infusion	Refractory Metastatic Colorectal Cancer	R	The Third Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China	Early Phase 1
NCT05410717	PB	Biological: Claudin6 targeting CAR-NK	Stage IV Ovarian Cancer	R	The Second Affiliated Hospital of Guangzhou Medical University	Phase 1 Phase 2

		cell	Testis Cancer, Refractory Endometrial Cancer Recurrent CAR NK		Guangzhou, Guangdong, China Guangzhou, Guangdong, China	
NCT05247957	U	Biological: CAR-NK cells	Safety and Efficacy	R	Hebei Yanda Lu Daopei HospitalSanhe, Hebei, China	Phase 1
NCT05472558	cord blood	Biological: anti-CD19 CAR-NK	B-cell Non Hodgkin Lymphoma	NY	2nd Affiliated Hospital, School of Medicine, Zhejiang University Hanzhou, Zhejiang, China	Phase 1
NCT04623944	U	Biological: NKX101—CAR NK cell therapy	Relapsed/Refractory AML AML, AdultMDS Refractory Myelodysplastic Syndromes	R	Colorado Blood Cancer Institute Denver, CO, USA Winship Cancer Institute, Emory University Atlanta, GA, USA University of Chicago Medical Center Chicago, IL, USA (and 4 more)	Phase 1
NCT05410041	U	Biological: CAR-NK-CD19 Cells	Acute Lymphocytic Leukemia Chronic Lymphocytic Leukemia Non Hodgkin Lymphoma	R	Beijing Boren Hospital Beijing, Beijing, China	Phase 1
NCT05336409	U	Biological: CNTY-101 Biological: IL-2 Drug: Lymphodepleting Chemotherapy	R/R CD19-Positive B-Cell Malignancies Indolent Non-Hodgkin LymphomaAggressive Non-Hodgkin Lymphoma	NY		Phase 1

Abbreviations: U - unknown, PB - peripheral blood, UK - unknown, R - recruiting, NY - not yet recruiting.

Conclusion

Through this research it is evident that CAR-T cell therapy is a concept that has a lot of potential to grow and branch out. In the future, it is expected that there to be various different types of CAR-T cell therapy with distinct. This will be extremely beneficial in properly treating cancers like multiple myeloma, as it allows for numerous options and personalized approaches for each patient's case. The future of CAR T-cell therapy likely lies in optimally powerful CARs with multivalent antigen specificity, minimizing toxicity to healthy cells—a crucial concern in current CAR treatments. Taking the concept of CAR-T, the development of CAR-NK may also grow. While it might not be as strong, it is a much more general treatment that doesn't need to be specific, making it more convenient and efficient. Dual antigen specificity could further enhance disease outcomes by

enabling the targeting of a broader range of cancer cells. New technologies are allowing for new discoveries such as this treatment, always leaving many possibilities for the next groundbreaking biomedical discovery.

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