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CAR-T vs CAR-NK cells: an integrative review of therapeutic approaches in immunotherapy

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ABSTRACT

CAR-T and CAR-NK cells are immune cells modified in the laboratory to express a chimeric antigen receptor, which allows them to recognize and specifically attack cancer cells, obtaining efficacy in the treatment of certain types of cancer, especially hematological ones. The objective of this systematic review is to report the use of CAR-T and CAR-NK cell treatment, its pros and cons, to describe its manipulation process and its application in patients. The methodology of this study is a systematic review using the MEDLINE, PubMed, and CAPES databases to search for articles that addressed CAR-T and CAR-NK cells, published between 2020 and 2022, using the keywords CAR-T cells and immunotherapy and neoplasm and chimeric antigen receptors and natural killer cells. The main results were 463 reports. Of these, 12 met the eligibility criteria and were included in the study. Addressing the differences between CAR-T and CAR-NK, their advantages and disadvantages, the CAR manufacturing process, limitations of the two therapies, their manufacture and application in the patient. It is concluded that therapy with CAR-NK cells has been shown to have fewer adverse effects, have a wide option to be collected, and are more easily manipulated compared to CAR-T cells.

Keywords: CAR-T cells, Immunotherapy, Neoplasm, Chimeric antigen receptors, natural killer cells.

1 INTRODUCTION

Immunology is the science that studies the body's defense. This defense is called immunity, which is a set of specific and non-specific processes that occur in our body (AYRES, 2017). In this way, it prevents the entry of pathogenic agents through the recognition of the infectious process, acting in the elimination, regulation and immune memory. Immune responses are mediated by a variety of cells and by molecules that these cells express. Among them, two are used in immunotherapy for cancer treatment, being T lymphocytes and Natural Killer (NK) cells (RODRIGUES, 2022).

T lymphocytes act on the specific immune response, which according to Cruvinel *et al* (2010) is activated through antigens and produces defense cells, being responsible for cellular immunity due to the different subpopulations of T lymphocytes. Among the most studied

lymphocytes in the area of immunotherapy, cytotoxic TCD8+ stands out, which are capable of causing the death of defective cells, such as cells infected by viruses or tumor cells. Natural Killer (NK) cells, on the other hand, originate in the bone marrow and are responsible for cytotoxicity against some target cells, acting mainly against virus-infected cells, immunoglobulin G (IgG)-coated cells, and tumor cells (RODRIGUES, 2022; BARARDI *et al* , 2010; GOUDOURIS *et al* , 2017).

Immunotherapy is mainly used in the treatment of various malignant neoplasms, where the antitumor effect of the immune system is used, allowing the body's cells to recognize the tumor and attack it, causing it to regress, and can even be eliminated. This therapy is a personalized treatment, focusing only on cancer cells, unlike broad therapies that do not only target the tumor, but also healthy cells. However, immunotherapy is not without adverse effects(BANDARA *et al*, 2023; FREIRE, 2019; BRITO, 2022).

With the advancement of immunotherapy, new forms of treatment have also emerged, such as CAR-T cells, where its premise is to strengthen the immune response and attack cancer through T cells, and more recently CAR-NK cells. (SOUSA *et al*, 2019; GONÇALVES et al, 2022).

The objective of this systematic review is to report the use of CAR-T and CAR-NK cell treatment, its pros and cons, to describe its manipulation process and its application in patients.

2 METODOLOGY

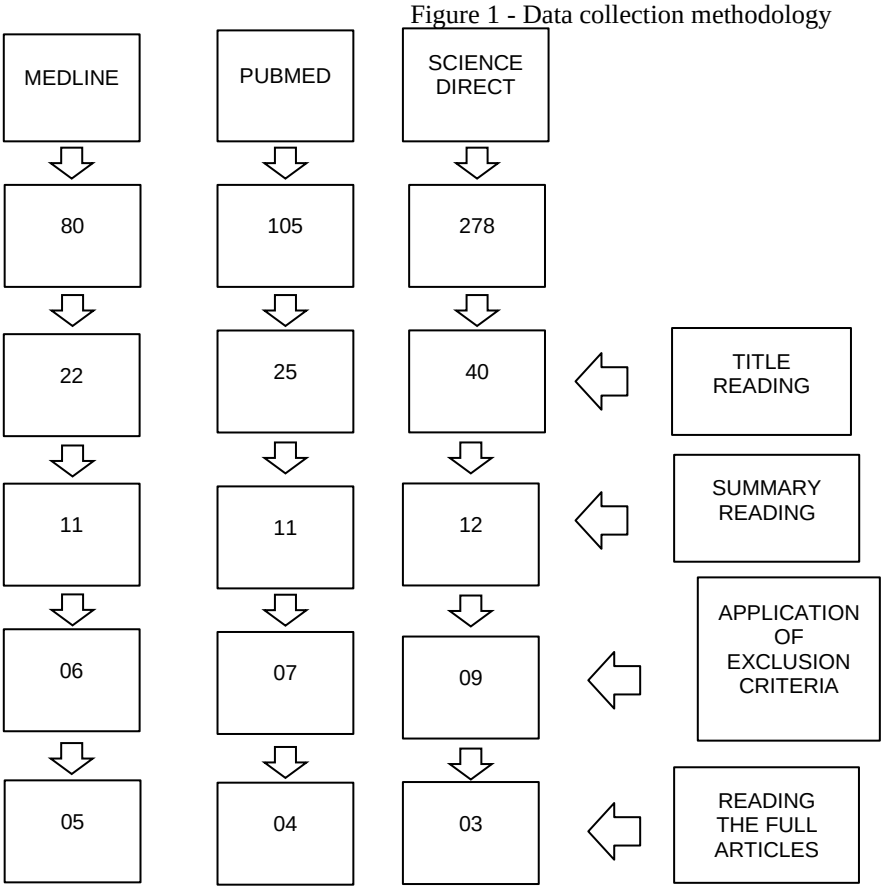
This is a systematic review, where data were obtained through the academic databases Medline, Pubmed, and ScienceDirect, with a time window of 3 years (2020 to 2022) being defined.

For the searches, the operator was used by booleando "and" with the keywords car-t cell and immunotherapy and neoplasm and chimeric antigen receptors and natural killer cell for searches in English; and CAR-T cells and immunotherapy and neoplasia and chimeric antigen receptors and natural killer cells for searches in Portuguese.

A data collection methodology was constructed with the result showing the process of selecting the articles, contained in the image below (Figure 1). The selection was carried out in 3 stages, where in the first it was with the search for keywords, placing the filters "year of publication", "language" and the desired platform, then separating the articles through the themes and reading the abstracts. The second stage was the full reading of the articles, selecting only those that were related to the theme and that made sense with the article's proposal. And the third stage was the elimination of articles that will be repeated and that did not adhere to the theme.

In the end, there were 12 articles in the portfolio, all of them in English. The presentation of the results was made using Microsoft Excel Office 2019 spreadsheets, with descriptive data, graphs and tables.

Figure 1 - Data collection methodology



Source: The authors, 2024.

3 RESULTS

AUTHOR/ YEAR OF PUBLICATION	ARTICLE TITLE	ARTICLE SUMMARY
1 - Hongwen Li, Wenting Song, Zhaoming Li e Mingzhi Zhang - Ano 2022	*Preclinical and clinical studies of CAR-NK cell therapies for malignancies *Preclinical and clinical studies of CAR-NK-cell therapies for malignancies.	The main differences between CAR-T and CAR-NK cells: CAR-T has great progress with hematological malignancies, has a very high neurological toxicity, in addition to the time and manufacture being time-consuming, harming diseases with rapid advances. CAR-NK have a great advantage in solid tumors, having a lower neurological toxicity and showing resistance against viral infection.
2 - Tamara J. Lasover, Alexander Biederstädt and Katayoun Rezvani - Ano 2022	*Natural killer cells in immunotherapy with antitumor adoptive cells *Natural killer cells in antitumour adoptive cell immunotherapy.	Cell therapy using CAR-T cells is a promising approach for the treatment of hematologic and solid malignancies, but some challenges have been faced. Natural killer cells, on the other hand, do not present the same risks that have so far demonstrated a favorable safety profile.
3 - Junfeng Chu, Fengcai Gao, Meimei Yan, Shuang Zhao, Zheng Yan, Bian Shi e Yanyan Liu - Ano 2022	*Células natural killer: uma imunoterapia promissora para o câncer. *Natural killer cells: a promising immunotherapy for cancer.	In the search for solid tumors, the most targeted are CAR-NK cells that express antigens associated with tumors, in addition to not showing an association with cytokine release syndrome, neurotoxicity and GVHD. CAR-NK can be acquired from the umbilical cord, bone marrow, embryonic or pluripotent stem cells. Some studies are being done to use allogeneic or autologous NK cells.
4 - Ewa Wrona , Maciej Borowiec e Piotr Potemski - Ano 2021	*CAR-NK cells in the treatment of solid tumors *CAR-NK Cells in the Treatment of Solid Tumors.	For the construction of CAR-NK cells, it is necessary to incorporate the DNA strand with a template prepared for the construction of the CAR. For production, CAR-NK can be acquired from several sources, and depending on the origin, it can interfere with the antitumor efficacy, but as its cytotoxic capacity is modified and maximized, its persistence in the blood increases. In addition, it was shown that CAR-NK cells from donors remained in the blood longer, leaving an incentive for more clinical trials.
5 - Michael A. Morgan, Hildegard Büning, Martin Sauer e Axel Schambach - Ano 2020	*Use of cell and genome modification technologies to generate improved "off-the-shelf" CAR T and CAR NK cells. *Use of Cell and Genome Modification Technologies to Generate Improved "Off-the-Shelf" CAR T and CAR NK Cells.	T cell activation is performed after recognition and binding to foreign peptides, while NK cells are activated depending on the balance of activation and inhibition signals. Strategies such as overcoming tumor immune escape mechanisms and genomic engineering can be applied to generate ready-to-use CAR cell therapies. Some products are being studied as potential ready-to-use cellular products.
6 - Mireia Bachiller, Lorena Pérez-Amill, Anthony Matthew Battram, Sebastián	*NK cells enhance the anti-tumor efficacy of CAR-T cells by improving the formation of immune/tumor cell	The study in question demonstrates the efficacy of using CAR-NK and CB-NK cells with CAR-T cells for some specific tumours, increasing their

Ciro Carné, Amer Najjar, Els Verhoeyen, Manel Juan, Álvaro Urbano-Ispizua and Beatriz Martín Antônio - Year 2021	clusters and improving the fitness of CAR-T cells. *NK cells enhance CAR-T cell antitumor efficacy by enhancing immune/tumor cells cluster formation and improving CAR-T cell fitness.	efficacy without increasing neurotoxicity and CRS.
7 - Ying Gong , Roel GJ Klein Wolterink , Jianxiang Wang , Gerard MJ Bo e Wilfred TV Germeraad - Ano 2021	*Chimeric antigen receptor (CAR-NK) natural killer cell design and engineering for cancer therapy. *Chimeric antigen receptor natural killer (CAR-NK) cell design and engineering for cancer therapy.	Recommendations for the use of genetic elements for better improvement of CAR-NK were described, with minor adverse effects and increasing improvement and with a stronger antitumor response.
8 - Agisilaos Balatsoukas, FilippoEegnoli and Khalid Shah - 2022	*NK cells in the brain: implications for the development and therapy of brain tumors. *NK Cells in the Brain: Implications for Brain Tumor Development and Therapy.	NK cells used for brain tumors are mediated by chemokine that act on the NK cell receptor having a better effect on the tumor. CAR-NK cells offer some advantages such as the independence of antigen presentation by MHC molecules, safety for allogeneic use being suitable for immediate use, in addition to reducing the risk of GVHD, cytokine release syndrome and neurotoxicity.
9 - Guozhou Tsai, Han Dong, Yong Liang, James Dongju Ham, Romi Rizwan A. Jianzhou Chen - Ano 2020	*CAR-NK cells: a promising cellular immunotherapy for cancer. *CAR-NK cells: A promising cellular immunotherapy for cancer.	Cellular immunotherapy is a new treatment that aims to take advantage of the immune system to eliminate cancer, such as the use of CAR-NK cells. Firstly, the safety in the use of CAR-NK cells is better than CAR-T cells. Second, CAR-NK cells can eliminate tumors independent of CAR. And thirdly, CAR-NK cells can be produced and taken from a variety of sources. Recently they are building specific CAR for NK cells, where they are exhibiting varied effects related to cytotoxicity and cytokine production.
10 - Ahmet Yilmaz, Hanwei Cui, Michael A. Caligiuri e Jianhua Yu - Ano 2020	* Natural killer cells engineered by chimeric antigen receptor for cancer immunotherapy. *Chimeric antigen receptor-engineered natural killer cells for cancer immunotherapy.	The study of CAR-T cells for other types of tumors has increased, but after reports of serious side effects with this therapy, the studies were stopped. NK cells, on the other hand, offer some advantages against cancer, such as not needing a complete match, causing little or no graft versus host disease, immunological between the donor and the patient, and thus generating a potential for ready-to-use products.
11 - Urvi A Shah, Sham Mailankody - Ano 2020	*CAR T and CAR NK cells in multiple myeloma: expanding targets. *CAR T and CAR NK cells in multiple myeloma: Expanding the targets.	Although studies are being very promising on CAR-T and CAR-NK cells, caution should be exercised, as most had remission, but without cure and eventually relapsed. Much research still needs to be done because there are many obstacles, such as cost, adverse effects, and competitiveness with other types of immunotherapies that may have other benefits and facilities.

12 - Anahid Jewet, Janko Kos, Kawaljit Kaur, Tahmineh Safai, Christine Sutant, Wang Chen, Paul Wong, Artin Keshishian Namagerdi, Chhang Fang, Yuman Fong, Meng-Wei Ko - Ano 2020	*Natural killer cells: various roles in tumor immunity and defects in the preneoplastic and neoplastic stages of tumorigenesis. *Natural Killer Cells: Diverse Functions in Tumor Immunity and Defects in Pre-neoplastic and Neoplastic Stages of Tumorigenesis.	NK cell anergy is defined as selective loss or decreased cytotoxicity when cytokine and chemokine secretion increases. T cell anergy, on the other hand, have their functions inhibited. It is already well established that in cancer patients there is a suppression of NK cell function, but it is not known for sure if this suppression occurs because of cancer induction and progression or if NK cell function happened before cancer establishment. One strategy that is being widely studied is the use of joint cancer treatments such as immunotherapies mixing chemotherapy strategies for the complete eradication of cancer.

Source: The authors, 2023.

4 DISCUSSION

The composition of the results was formed by a portfolio with 12 articles. They present CAR-T and CAR-NK cells as very promising techniques in the treatment of some types of cancer. Articles 01 to 08 collected in this review present the general aspects of this technology and point out the main differences between CAT-T and CAR-NK cells, in addition to exploring the main advantages, especially when it comes to CAR-NK cells. Side effects and adverse reactions are also highlighted in these articles.

Articles 09 and 10 deal with the manufacture of the Chimeric Antigen Receptor (CAR). Finally, studies 11 and 12 deal with the limitations and precautions in the use of these therapies.

In view of this general picture, the results were categorized for a better presentation.

4.1 CHIMERIC ANTIGEN RECEPTOR (CAR)

T and NK cells that are designed to express CAR continue to eliminate target cells with the same mechanism as unmodified cells, but their cytotoxic action is increased. As well as Yilmaz *et al*. (2020) describes, the chimeric antigen receptor is hybrid, having an antibody region with a T-cell receptor region, containing an extracellular site designed to bind to the antigen, a hinge region, a transmembrane domain, which may have one or more costimulators, and a signaling one, for the induction of cytotoxicity after binding with an antigen. A tumor antigen ligand can be used in some CARs (MORGAN *et al*, 2020; LU *et al*, 2022).

In addition, Xie *et al*. (2020) point out that the first tests with CAR-NK cells were carried out using the CAR designed for T cells. However, nowadays specific CAR is already being performed for NK cells, this modification makes it possible to obtain more effective results, such as the improvement of their potency and cytotoxicity (MAROFI *et al*, 2021).

Silva et al. (2021) describe that viral techniques such as the retro or lentiviral method are used to modify the cell. In both cases, there is a transfer of genes encoding the CAR to the cell in question, where the action of translating, transcribing and transferring to its cytoplasmic membrane will be carried out. And the non-viral technique is a method that integrates the target transposon in the same way as the viral method, but being a more accessible, faster and more effective alternative. Thus, after the modification is successful, the cells can be expanded in vitro and undergo quality control to be selected.

On the other hand, Ramos et al. (2021) specify that there is a small difference between retroviral and lentiviral vectors, lentiviral vectors can insert genetic material into cells that do not divide, while retroviral vectors pass on the material only to dividing cells. And in relation to non-viral CAR, a DNA sequence called transposon is used, which has the ability to change the position of DNA within a genome through the extirpation and introduction of genetic material.

4.2 CÉLULAS CAR-T

Treatment with CAR-T cells is part of the group of cancer therapies that are part of immunotherapy and involves the manipulation and reprogramming of autologous antitumor T lymphocytes, that is, the patient's own or allogeneic, being from a donor, where the surface of chimeric antigen receptors (CARs) is expressed, allowing the antitumor action to be directed to the recognition and elimination of the tumor (ABREU, 2018; GONÇALVES *et al*, 2017).

CAR-T cells are bringing great results in relation to hematological tumors, thus bringing other treatment options, attacking these tumor cells through cytoplasmic costimulation, cytokine secretion, T cell proliferation, and tumor cell cytolysis (NARDO *et al*, 2021). CAR-T therapy has brought exciting results, but CAR-T cells used in solid tumors no longer present the same results, mainly due to their high molecular complexity, clonal and different anatomical locations, with their main difficulties being the infiltration of the solid tumor and the duration of these cells long enough in the body to generate an efficient response (SILVA et al, 2005). Its greatest advantages include low relapse rates precisely because its effectiveness lasts for years, the infusion is performed only once due to the sudden intervention that occurs in the body (ZILIG et al, 2018).

It contains some serious side effects and drawbacks that occur during therapy, including cytokine release syndrome (CRS), where an inflammatory process is observed because of very high levels of cytokines induced by CAR-T cells and the target antigen (CLÉ *et al*, 2021). Immune effector cell-associated neurotoxicity syndrome (ICANS) where they present hallucinations, headaches, aphasia, ataxia, dimetry, paresis, somnolence, seizures and in more severe cases can

progress to encephalopathy. Hypogammaglobulinaemia due to cytotoxic effect outside the tumor. Tumor lysis syndrome (TLS) occurs after the destruction of malignant cells and their contents are released into the extracellular space, which can lead to acute kidney injury. And graft-versus-host disease (GVHD) is characterized by hepatitis, abdominal pain and diarrhea (DARMON *et al*, 2008; YILMAZ *et al*, 2020; MORGAN *et al*, 2020; SOARES *et al*, 2022; MARQUES *et al*, 2022).

For Huang *et al.* (2022), CAR-T cell therapy was revolutionary for immunotherapy even though there are limitations, several studies are being carried out to solve them. In the same vein, Morgan *et al*. (2020) cite that even with this improvement research, CAR-T cells have paved the way for other cells that can be used with CAR, such as Natural Killer cells.

4.3 CÉLULAS CAR-NK

The discovery of other types of cells that can also attack tumor cells has aroused great interest, especially NK cells that already have the ability to eliminate tumor cells without the need for modification. By using NK cells expressing CAR, everyone was very hopeful, because the use of NK cells brought good results (SCHMIDT *et al*, 2021).

Li (2022) comments that NK cells have become an alternative to T cells precisely because of their advantages in terms of decreased cytotoxicity, graft-versus-host disease (GVHD), and adverse events, making CAR-NK therapy promising. Laskowski *et al*. (2022) state that NK cells recognize their target independent of human leukocyte antigen, as their function is controlled by a set of activating and inhibitory receptors that help distinguish between healthy and stressed cells , emitting a "kill" or "do not kill" signal, thus reducing DNA damage or malignant mutation.

According to Schmidt *et al*. (2021), NK cells can be taken from different places in the body, which are from peripheral blood that are easier to isolate, but more difficult to manipulate; Through stem cells and through the umbilical cord being more easily manipulated (CB-NK). Bachiller *et al*. (2021) address that CB-NK cells are defined to obtain "ready-to-use" NK cells, in addition to CB-NK demonstrating an improved antitumor action, and can also be used to improve the efficacy of CAR-T cells. Corroborating this understanding, Balatsoukas *et al*. (2023) state that the placenta can also be used as a source of NK cells, and it is possible to use it as a "ready-to-use" source.

In the same context, Teng *et al. (*2023) describe that, compared to CAR-T cells, CAR-NK cells do not cause severe toxicities, do not cause cytotoxicity, their preparation time is shorter, have a greater potential to be produced ready for use, thus reducing manufacturing time and costs,

in addition to being possible to freeze, store, thaw, and administer them without harming NK cells (WRONA *et al*, 2021).

On the other hand, SCHMIDT *et al*. (2021) also address that even though CAR-NK cells are easy to deal with and have fewer adverse effects, there are still difficulties and characteristics that are complicated to solve, such as the introduction of genetic material into NK cells, and after the introduction of genetic material, it is necessary to carry out the expansion, but there is also a difficulty in achieving this expansion.

4.4 PRODUCTION AND INFUSION PROCESS

Before performing the infusion in the patient, it is necessary to perform five steps for the production of both CAR-T cells and CAR-NK cells. Ramos et al. (2024) clarify that in the first stage, initially, it is necessary to collect unstimulated leukocytes from the patient, through leukapheresis in large volume. In the second stage after collection, the separation of T cells occurs, which can be through the removal of red blood cells, division of cells by size and density, or the elimination of monocytes and the isolation of lymphocytes. Then, in the third stage, they are sent to a cell processing center where the T cells or NK cells are isolated and activated with viral vectors that encode the CAR and introduce the RNA, which is transcribed into DNA, which recombines with the genome of the T or NK cell and permanently incorporates the CAR gene. In the fourth stage, reprogramming occurs to express the CAR, where the vector, which has the genetic material, will bind to the cell and thus introduce this genetic material.

After the gene modification step, in the last step the cells already containing CAR are expanded in vitro, and the cell itself will divide and CAR expression is maintained. At the end of this process, they are frozen and delivered to be transfused into the patient. This process from production to delivery to the patient takes around 2 months, which makes treatment difficult for patients who have a rapid progression of the disease, requiring the use of other therapies until the arrival of CAR-T cells (SOARES, 2018; SOARES et al, 2022).

To perform the infusion, CLÉ et al. (2021) explain that it will be necessary to hospitalize the patient and monitor vital signs. Have emergency materials available if necessary. Transfusion equipment that does not have a leukocyte filter should be used, a premedication of paracetamol and antihistamine should be administered to the patient within 60 minutes before the infusion, at no time is the infusion of other medications allowed in conjunction with the CAR-T or CAR-NK cells, and rapid infusion is recommended, around 30 minutes. Carry out the follow-up of the patient

within the hospital environment for at least two weeks and after this period he is released to leave the hospital as long as he stays up to two hours away for at least one month for monitoring.

5 CONCLUSION

Immunotherapy with CAR-T and CAR-NK cells show promise in the treatment of cancer, standing out for its efficacy in eliminating tumor cells and its advantages over conventional therapies. While CAR-T cells demonstrate success in certain hematologic cancers, they face challenges in solid tumors, due to molecular complexity and infiltration difficulties. On the other hand, CAR-NK cells suggest as an attractive alternative, offering efficacy in the elimination of solid tumors, with lower cytotoxicity and reduced adverse effects. Although the production process is complex, CAR-NK shows potential to reduce costs and manufacturing time, however, challenges persist, such as its safety and long-term effectiveness. Thus, it is crucial to continue with the research and development of these therapies to provide more effective and personalized treatment options for cancer patients.

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