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Review - Human and Animal Health

What is the Best Option for Cellular Immunotherapies in Triple-Negative Breast Cancer? A Systematic Review Based on *in vitro* and *in vivo* Evidences

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HIGHLIGHTS

- Triple-negative breast cancer has the worst prognosis and high malignancy.
- Immune cell-based immunotherapies are potentially more effective against solid tumors like triple-negative breast cancer (TNBC).
- CD4 lymphocyte therapy achieved the greatest tumor reduction among the selected approaches.

Abstract: Triple-negative breast cancer (TNBC) is the breast cancer subtype with the worst prognosis and highest malignancy. As an alternative treatment, immunotherapy has gained prominence in recent years for its use of components that modulate the patient's own immune system to combat cancer. Although approved therapies using monoclonal antibodies have shown limitations, a more promising alternative for TNBC is the use of immune cells, which have the ability to infiltrate solid tumors and remain in the tumor microenvironment long-term, promoting a localized and effective immune response. The present study proposed a systematic review of cellular immunotherapies currently under investigation for TNBC. The review was registered with PROSPERO (CRD42024591409). Studies were selected using the PRISMA strategy, and the risk of bias in *in vivo* studies was assessed with the SYRCLE tool. A total of six studies with *in vitro* and *in vivo* analyses were included. Among these, 50% evaluated CAR-T therapy (Chimeric Antigen Receptor T Cells), 16.6% CAR-M therapy (Chimeric Antigen Receptor Macrophages), 16.6% dendritic cell vaccines, and 16.6% autologous $CD4^+$ T lymphocytes stimulated ex vivo. The *in vitro* analyses focused on antitumor capacity, cell proliferation, cytokine production, apoptosis, and phagocytosis. For the *in vivo* analyses, tumor growth, survival, metastasis development, and cellular infiltration were evaluated. All therapies demonstrated promising effects; notably, immunotherapy with autologous $CD4^+$ T lymphocytes achieved the greatest tumor reduction among the studied therapies. This review highlights the potential of immune cell-based therapies, particularly $CD4^+$ T lymphocytes, emphasizing the need for further research and potential human testing.

Keywords: Triple-negative breast cancer; immune cells; tumor microenvironment; target therapy.

INTRODUCTION

Breast cancer is the malignant disease with the highest mortality rate due to neoplasia among women worldwide [1]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) [2]. This neoplasia constitutes 15 to 20% of breast cancers and presents a worse prognosis compared to other subtypes, with high rates of recurrence and mortality [3].

Due to the absence of receptors that are typically targeted by alternative therapies in other breast cancer subtypes, TNBC is considered the most unfavorable and aggressive subtype, limited to chemotherapy as the standard treatment, necessitating the development of more specific new therapies [4]. In search of more specific treatments, the use of immunotherapies has emerged as a promising approach [5]. The goal of immunotherapies is to manipulate the immune system to eradicate malignant cells while preserving the functional integrity of normal cells in the body [6]. Various drugs have been developed with this goal, such as checkpoint modulators, monoclonal antibodies, vaccines, and chimeric antigen receptor (CAR) T-cell therapies, demonstrating significant efficacy in cancer treatment [7].

The key point for developing immunotherapies for breast cancer is manipulating the tumor microenvironment (TME), a complex environment capable of developing mechanisms that favor tumor progression [8]. Among these mechanisms, immunosuppression triggered by tumor-associated macrophages (TAMs) with an M2-like phenotype and regulatory T cells, which favor immune evasion by inhibiting the pro-inflammatory action of T lymphocytes and secreting suppressive cytokines such as IL-10 and TGF-β, is the main challenge [9].

Given the significant involvement of immune cells in the TME, their use in immunotherapy appears promising, particularly in solid tumors [10]. Adoptive cell therapy (ACT), especially using CAR-T cells, has gained considerable attention in recent years, proving that immune cells can serve as an effective therapeutic against cancer [11]. Besides T cells, researchers have been working on engineering techniques with other cell types, such as macrophages (CAR-M), NK cells, and dendritic cells (DC), which could infiltrate solid tumors and remain in the tumor microenvironment long-term, generating a local and effective immune response against solid tumors [12].

Currently, among the existing immunotherapies for TNBC, two types of antibodies were approved in 2021: the monoclonal antibody Pembrolizumab (Keytruda) that binds to the PD-L1 receptor, and an antibody-drug conjugate called sacituzumab govitecan (SG) targeted at Trop2 (Trodelvy) for patients with advanced disease undergoing chemotherapy [4]. Regarding the use of specific cell therapies for TNBC, researchers have been striving, but it remains a challenge [13].

Thus, we propose a systematic review to provide an update on the main cellular immunotherapies that have been studied to treat TNBC, as well as the challenges and perspectives of this type of treatment, through *in vitro* and *in vivo* scientific evidence.

MATERIAL AND METHODS

Search strategy

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14,15] and is registered in the PROSPERO database under the identifier CRD42024591409. A two-step search strategy was developed to maximize the retrieval of relevant search records. The first step involved an advanced search of two comprehensive electronic databases: PubMed/Medline (www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.scopus.com). In the second step, the reference lists of all studies identified in the databases were carefully screened to find additional studies potentially relevant for inclusion in the systematic review [16-18]. In both steps, two researchers independently searched for original articles investigating the application of cellular immunotherapies in triple-negative breast tumors.

The advanced search applied to the databases was based on specific filters developed from three components: pathology, methodology, and treatment. Initially, a search filter for PubMed/Medline was developed according to standardized descriptors (MeSH terms) organized in a hierarchical format for the MeSH database (www.ncbi.nlm.nih.gov/mesh). To enhance the retrieval of relevant indexed and indexing studies, the commands [MeSH Terms] and [TIAB] were combined. The same search matrix used in the

PubMed/Medline database was adapted for Scopus, using the TITLE-ABS-KEY search algorithm [16-18]. To reduce search noise, standardized limit algorithms were applied to exclude review articles and book chapters in both databases. A language restriction (English) and a search for articles from the last 5 years were applied to the search strategy (Supplementary Table 1).

Study eligibility criteria

Two reviewers independently assessed the potentially relevant studies. Initially, the specific publication data (authors, journal, volume, issue, edition, and year) as well as the titles and abstracts of all articles extracted from the electronic databases were evaluated. Duplicate studies were excluded, and only experimental studies (*in vitro* and *in vivo*) that analyzed the use of cellular immunotherapies against triple-negative breast cancer were subjected to eligibility analysis and considered for inclusion in the review. In cases of disagreement in the study evaluations, a third reviewer was involved.

After the initial screening, all relevant findings were retrieved in full text and assessed for eligibility. Study exclusion was based on well-defined criteria: (a) studies that did not use triple-negative breast cancer as the pathology; (b) studies that did not work with cellular immunotherapy; (c) full text unavailable; (d) secondary studies (editorials, commentaries, letters to the editor, literature reviews without original data); and (e) grey literature (studies published in non-indexed or non-peer-reviewed journals). The reviewers independently analyzed the eligibility criteria, and all doubts were resolved by consensus through discussion. To extend the retrieval of relevant studies, reference lists of selected articles were also manually screened for potentially relevant articles.

Extraction and synthesis from *in vitro* and *in vivo* studies

Qualitative and quantitative data were extracted using structured tables. Each table was constructed based on the basic methodological requirements used to characterize the studies according to different descriptive levels such as: (i) publication characteristics: authors, year, and country; (ii) characteristics of the experimental model: species studied; (iii) type of tumor cell used; (iv) volume of tumor cells used; (v) characteristics of the treatment cell model; (vi) characteristics of the immunotherapy treatment such as route of administration, cell volume, and number of doses; and (vii) main results obtained: antitumor and immunological effects, reduction in tumor volume and metastasis, considering adverse effects, and any other important findings.

The characteristics described in (i), (ii), (iii), (iv), and (vii) were also obtained and analyzed in the *in vitro* studies, in addition to (viii) main analyses performed such as cytokine production, flow cytometry, cell expansion and exhaustion, and other important analyses. Finally, the research results were grouped.

Risk of bias assessment of *in vivo* studies

The risk of bias in animal studies was assessed using the SYRCLE (Systematic Review Center for Laboratory Animal Experimentation) methodology [19]. This method is based on the Cochrane Collaboration's tool for analyzing the level of bias in randomized trials and is adapted to address bias aspects specific to animal studies [20]. To enhance transparency and applicability, standardized signaling questions guide the judgment of systematic review assessors based on the following domains: (i) sequence generation, (ii) baseline characteristics, (iii) allocation concealment, (iv) random housing, (v) blinding, (vi) random outcome assessment, (vii) incomplete outcome data, (viii) selective outcome reporting, and (ix) other sources of bias. Two assessors independently evaluated the risk of bias for each study, and in cases of disagreement, a third assessor was involved. Adherence to SYRCLE's individual quality criteria was graphically represented [21].

Statistical analysis

Each evaluation and comparison were performed thoroughly and repeated at least twice, showing consistent results, and the figures presented reflect data from a representative analysis against the analyzed products. Graphing and data interpretation were performed using GraphPad Prism® 8.0 (GraphPad Software, Inc, La Jolla, CA, USA). For nonparametric variables, the comparison of means was performed using the t-test when evaluating two means or by one-way ANOVA followed by Tukey's post-test. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

PRISMA guideline

In the PubMed/Medline and Scopus databases, 5.008 articles were identified. Of these, 4.038 were eliminated after analyzing the title and/or abstract because they were not related to the topic, leaving 970 articles. Of these, 964 were excluded for various reasons: they did not address cellular immunotherapy as a topic, were not related to triple-negative breast cancer, or were letters to the editors or literature reviews. After all exclusions, only 6 studies were included in the systematic review. All studies presented both *in vivo* and *in vitro* analyses. The flowchart of each step in the selection process is shown in Figure 1.

General characteristics of the studies

Regarding the geographical origin of the studies included in this review, most (83.3%) originated in China [2,10,22-24]. Only one study [25] was conducted in Denmark (16.6%).

All studies indicated the origin of the tumor cells used for both *in vitro* analyses and for inducing the tumor *in vivo*, as well as the origin of the animal models and approval by the respective committees of each location. The articles with *in vivo* models were subjected to bias and quality assessment using SYRCLE-specific criteria (title, results, discussion, and publication quality), showing the percentage of items verified. The complete and stratified bias analysis by methodological items covered by the tool is shown in Supplementary Table 2. From this comprehensive analysis, all *in vivo* studies presented a low risk of bias, with an average of only 15.6% of criteria not met, as demonstrated in Figure 2.

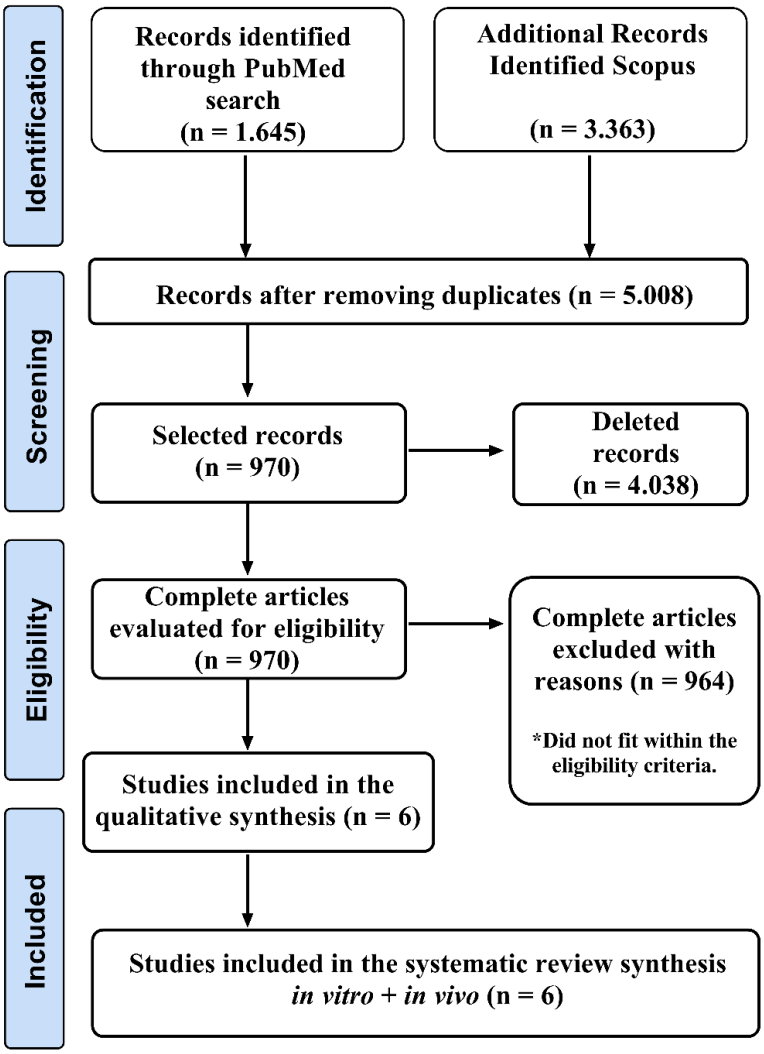

Figure 1. Systematic review flowchart with the steps of the methodology for obtaining articles based on the PRISMA statement. A total of 5.008 studies were found, 4.038 were excluded and 970 articles were analyzed for eligibility criteria. Among the 970 studies, 6 were selected for systematic review.

In vitro models

All studies used cell lines characterized as triple-negative breast cancer cells, with the most commonly used line being MDA-MB-231-LUC, a cell line derived from human mammary adenocarcinoma (66.6%; n = 4). One study [2] used both MDA-MB-231-LUC cells and MDA-MB-468 cells, which are derived from human breast carcinoma. Another line used was the 4T1 tumor cell line, derived from spontaneous mammary carcinoma in mice (33.3%; n = 2). The cell types and details of which studies used each cell line are described in Table 1.

Regarding the type of immune cell tested, the chimeric antigen receptor T cells (CAR-T) with specific targets were the most tested model (50%; n = 3) among the studies [2,10,23]. One article used therapy with ex vivo stimulated autologous lymphocytes, known as ALECSAT [25] (16.6%). Another study used a dendritic cell (DC) vaccine [22] developed with mimetic engineering transfected with miRNA-5119 (16.6%). The last study [24] used different models of chimeric antigen receptor macrophages (CAR-M) (16.6%). The main data from the selected articles and their key findings are presented in Table 1. Regarding the use of CAR-T therapy, the targets studied were: epidermal growth factor receptor (EGFR) [10], cluster of differentiation 24 (CD24) [2], and co-stimulatory protein B7-H3 [23].

In analyses with immune cells co-cultured with TNBC tumor cells, all immune cells were capable of recognizing and combating tumor cells, enhancing proliferative capacity, cytotoxicity, and the release of pro-inflammatory cytokines (IL-2, TNF-α, and IFN-γ). Xia and collaborators [10] analyzed EGFR expression in TNBC tumor cells by immunotransfer and through a cohort study from The Cancer Genome Atlas (TCGA), demonstrating that EGFR is highly expressed in this cell type compared to other cancers.

Regarding CAR-T targeting B7-H3, Zhang and collaborators [23], using BB-trlL2RB-z, also exhibited high cytotoxicity against TNBC tumor cells, along with high proliferative activity due to the presence of motifs related to STAT3 and STAT5 that enhance T cell proliferation Similar to CAR-T targeting B7-H3[2]. The expression of PD-1 on T cells was also assessed, which increased after co-incubation with CAR-T CD24, potentially limiting the use of this therapy.

The use of CAR-M [24] also showed promising results. The study developed five types of CAR-M with structural differences, defined as HmA, HmB, HmC, HmD, and HmE. The analyses demonstrated increased expression of MHC-II and CD86, as well as an increase in M1-type markers (Nos) and a decrease in M2-type markers (CD206 and Arg1). The HmC group was the most effective, with higher TNF-α production. Additionally, this CAR-M type HmC also showed lower apoptosis activity and higher phagocytic activity.

One study [22] reported satisfactory results with the use of mimetic engineering in DC vaccines transfected with miRNA5119 that, exhibited antitumoral effects against TNBC cells, increasing cytokine production such as IL-2, TNF-α, and IFN-γ and the proliferation of exhausted T cells, higher cytotoxicity, and reducing the number of PD-1-positive T cells.

The use of autologous peripheral $CD4^+$ T lymphocytes, in a therapy called ALECSAT [25], demonstrated expansion of T cells and NK cells, as well as a decrease in the viability of TNBC tumor cells, showing a favorable antitumoral profile.

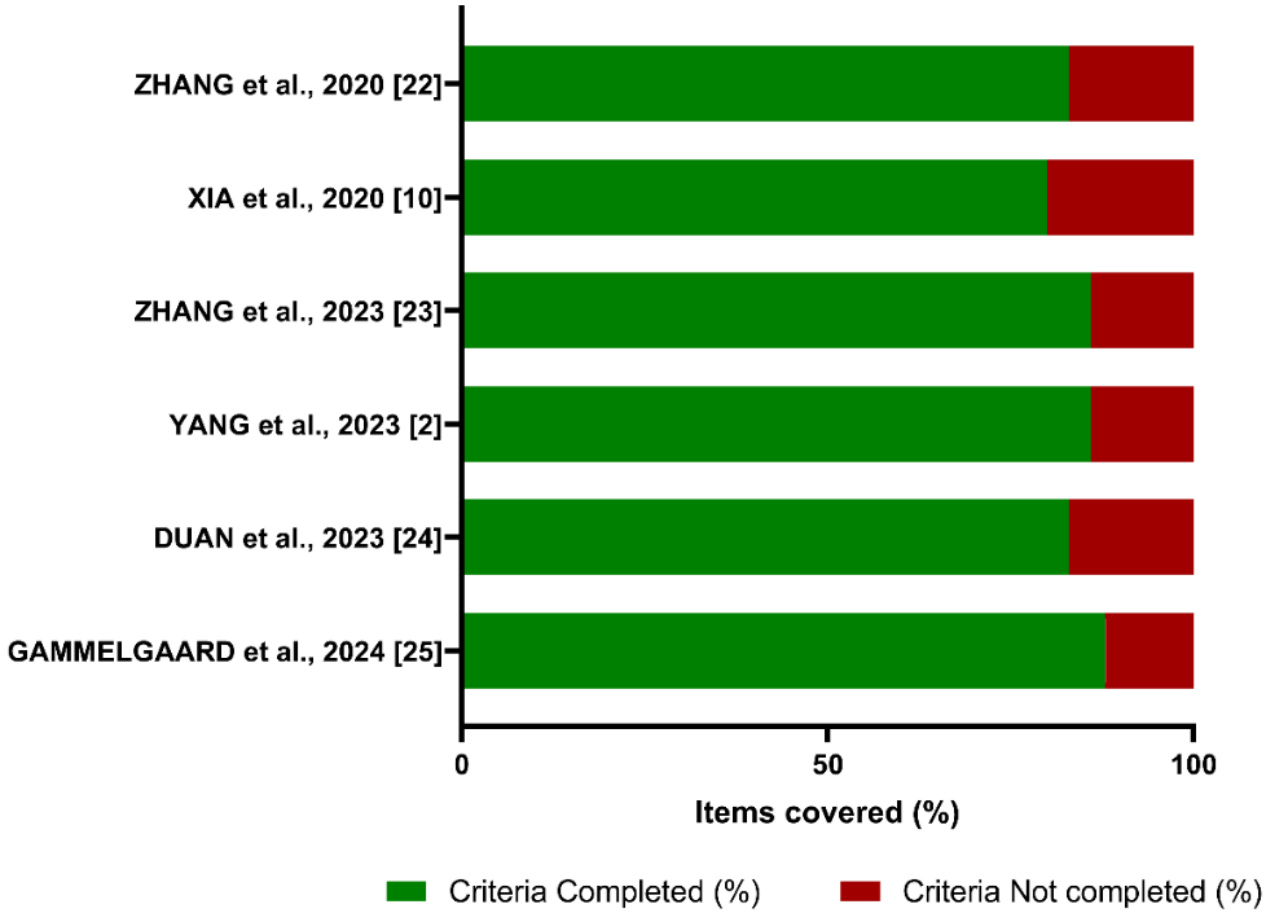

Figure 2. *In vivo* studies assessed against risk of bias criteria by the SYRCLE tool. Completed items are represented in green and non-completed items in red indicate potential risk of bias.

In vivo models

All studies used mice as the animal model. The most commonly used strain was BALB/c (50%; n = 3), followed by NOG immunodeficient mice (33.3%; n = 2) and severe combined immunodeficient (SCID) mice (16.6%; n = 1). All studies exclusively used female mice (100%; n = 6). The age of the mice ranged from 4 to 12 weeks, with most studies using animals between 6 and 8 weeks (50%; n = 3). Only one study reported the weight of the models (16.6%; n = 1). In all studies, the environmental conditions provided to the animals included housing in pathogen-free conditions with commercial feed and water ad libitum, a controlled light-dark cycle (12h light-12h dark, lights on from 06:00 to 18:00), and controlled temperature (21°C).

The tumor induction method in mice used in all studies was primarily direct injection of tumor cells into the mammary gland of the mice (100%; n = 6), with one study [25] also using patient-derived xenografts (PDX) in addition to this method (16.6%; n = 1). The most commonly used administration route for immunotherapies was intravenous (100%; n = 6), with two studies [2,25] also analyzing peritumoral administration (33.3%; n = 2). Regarding the frequency of administration, most studies (50%; n = 3) administered a single dose of the immunotherapy [2,25,23] followed by three doses (33.3%; n = 2) [24,22] and six doses (16.6%; n = 1) [10] in the smallest proportion. The main *in vivo* findings from the selected articles are presented in Table 2. All studies shared the common analysis of immunotherapies concerning tumor growth reduction (100%; n = 6). Three studies [10,23,25] also assessed the increase in animal survival following treatments.

The use of CAR-T therapy across different studies showed significant effectiveness in *in vivo* analyses [2,10,23] The authors reported results such as a decrease in tumor volume of approximately 68.52% (Figure 3). Additionally, a reduction in metastases, increased T cell infiltration, and no damage to other organs were observed. Xia and collaborators [10] also analyzed the survival of animals treated with CAR-T targeting EGFR, where treatment increased survival by 2.3 times, whereas Zhang and collaborators [23], using CAR-T targeting B7-H3, showed 1.1 times increase in survival.

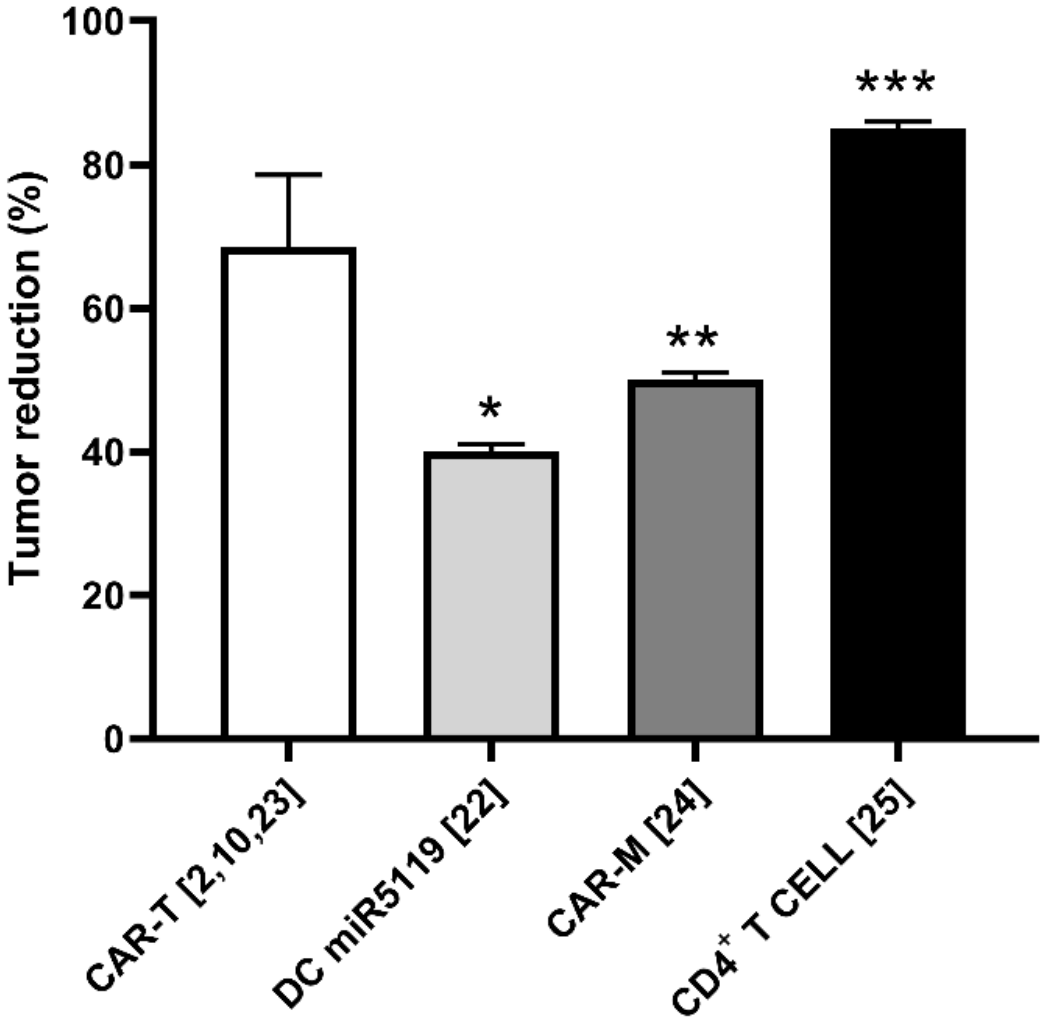

Figure 3. Tumor reduction rate (%) in animals treated with immunotherapies in different studies. $CD4^+$ T cell immunotherapy (black bar) shows greater tumor reduction compared to CAR-T (white bar), DC miR5119 (light gray bar), and CAR-M (dark gray bar). *p ≤ 0.05 compared to CAR-T, **p ≤ 0.05 compared to CARM, and DC miR5119, and ***p ≤ 0.05 compared to CAR-T, DC miR5119, and CAR-M.

Xia and collaborators [10] also examined the optimal dosage of CAR-T cells, as high doses can lead to cytokine release syndrome (CRS), which reduces tumor efficacy [26]. The study found that the average dosage (5×10^6) was the most effective and did not elevate pro-inflammatory cytokine levels. Furthermore, the treatment prevented pulmonary and liver metastases, while all control group animals exhibited metastases and no damage to tissues outside the tumor, demonstrating the therapy's specificity to tumor cells.

Regarding the CAR-T targeting CD24 proposed by Yang and collaborators [2], the efficacy of the immunotherapy was evaluated through two different administration routes, intravenous and peritumoral. It was observed that both routes had no difference in effects concerning tumor volume reduction, damage to other organs, T cell infiltration (immunohistochemistry), and the effector function of these cells, as analyzed through their products like Granzyme B and IFN-γ. Additionally, PD-1 expression was evaluated, showing increased expression after therapy, which may limit its use.

The study by Zhang and collaborators [23], also demonstrated that CAR targeting B7-H3 did not cause significant damage to other organs, nor did it lead to increased levels of circulating pro-inflammatory cytokines. Additionally, two days post-immunotherapy infusion, circulating T cells were still detected, suggesting significant duration.

One study [24] showed promising results with CAR-M. Among the developed structures, the HmmC type with TLR4 domain demonstrated the highest efficiency in both normal and immunodeficient mice, with a tumor volume reduction of approximately 50% after three doses, without observable side effects such as changes in animal weight or damage to other organs or local blood vessels.

The use of DC vaccines transfected with miRNA5119 [22] also yielded promising results. Analyses showed that administering the immunotherapy in a murine model led to a 40% reduction in tumor volume. Furthermore, the immunotherapy increased the number of effector T cells positive for IL-2, TNF-α, and IFN-γ, with higher cytotoxicity and a reduction in T cells positive for inhibitory receptors (PD-1, BTLA) and regulatory T cells (Treg), which are associated with immunosuppression.

Finally, one study [25] demonstrated that the combination of autologous peripheral $CD4^+$ T lymphocyte-based immunotherapy (termed ALECSAT) with anti-PD-L1 therapy yielded the most significant results among all studies reviewed. While ALECSAT alone led to a 20% reduction in tumor volume, its combination with anti-PD-L1 therapy resulted in a tumor volume reduction of approximately 85% (Figure 3). Additionally, the combined therapy group showed complete blockade of metastases, enhanced activation of T cell response pathways such as IL-2–STAT5, IFN-γ, and TNF-α, and a 1.3-fold increase in mouse survival compared to the monotherapy group.

DISCUSSION

This systematic review aimed to compile scientific evidence on the effects of immunotherapies using immune cells for triple-negative breast cancer (TNBC). To the best of our knowledge, this is the first study demonstrating the main therapies being explored in this area using this type of cell, considering current *in vitro* and *in vivo* studies.

The use of CAR-T has shown significant efficacy, especially in hematological tumors [27]. Most studies in this review utilized lentiviral vectors for genetic modification, ensuring stable expression of chimeric antigen receptors (CARs), which combine monoclonal antibody specificity with cellular activation to destroy tumor cells [28,29]. In TNBC, the Epidermal Growth Factor Receptor (EGFR), frequently overexpressed, is a promising target [30,31,32]. The primary physiological function of EGFR is to regulate epithelial tissue homeostasis, but in certain diseases, particularly cancer, it can drive tumorigenesis [33]. Xia and coauthors [10] developed EGFR CAR-T cells that reduced tumors and increased survival in preclinical models. However, cytokine release syndrome (CRS) and associated toxicities require dose adjustments to ensure safety [34]. EGFR blockade therapies, as demonstrated in a Phase 1 clinical trial for gallbladder carcinoma [35], showed efficacy but faced challenges related to off-target toxicity, including mucositis and skin lesions, underscoring the need for further studies to ensure safety.

Another relevant target in TNBC is CD24, a protein overexpressed in advanced stages of TNBC and associated with increased tumor growth and reduced survival [36,37]. Yang and coauthors [2] developed CD24-targeted CAR-T cells, demonstrating high cytotoxicity against TNBC *in vitro* and activation of apoptotic pathways *in vivo*, although PD-1 expression limited efficacy. Combining this approach with PD-1 inhibitors has demonstrated better effectiveness [38–41]. Zhang and coauthors [23] studied CAR-T targeting B7-H3, a protein overexpressed in cancer cells and tumor-associated macrophages (TAMs) involved in tumor progression [42]. Previous studies using CAR-T against the transmembrane protein B7-H3 showed positive antitumor effects in various cancers [43]. The authors integrated the CAR structure with a co-stimulatory receptor, 4-1BB, triggering a strong cellular immune response [44], and JAK/STAT pathways, responsible for stimulating immune cells [45]. This therapy, termed BB-trIL2RB-z (YRHQ), led to increased T-cell infiltration into the tumor microenvironment without elevated serum pro-inflammatory cytokine levels, as seen in a prior study involving prostate cancer cells. Additionally, it showed no toxicity to other animal organs [46]. These findings may be linked to the efficacy of adding the 4-1BB molecule, which can activate specific signals, enhancing inflammatory response activation and T-cell proliferation [47]. Notably, this result was observed at low doses, as higher doses led to increased pro-inflammatory cytokines. Thus, further studies are needed to determine the optimal dose, particularly in human trials.

Table 1. *In vitro* studies investigating antitumor effect of cellular immunotherapies against TNBC cells.

Study (author, year, and country)	Immune cell	Experimental model	Target molecule	Type of analysis	Main findings
Zhang et al., 2020, China [22].	4T1 tumor cell	DC transfected	miRNA 5119	Co-culture, flow cytometry, cell proliferation.	DC vaccines transfected with miR-5119 induce recovery of the immune response in exhausted $CD8^+$ T cells and enhance the release of pro-inflammatory cytokines (IL-2, TNF-α and IFN-γ) by exhausted T cells.
Xia et al., 2020, China [10].	MDA-MB-231-fluc	CAR-T	EGFR	Co-culture, flow cytometry, cell proliferation and cytotoxicity.	EGFR CAR-T cells exhibited high and specific cytotoxicity against TNBC, greater cell proliferation, stimulating the production of pro-inflammatory cytokines such as IL-2, IFN-γ and TNF-α, important for controlling the growth of malignant cells.
Zhang X et al., 2023, China [23].	MDA-MB-231-Luc-4	CAR-T	B7-H3	Co-culture, flow cytometry, cell proliferation.	BB-trIL2RB-z CAR-T cells showed increased proliferation and activation of T cells, due to the presence of motifs related to STAT3 and STAT5, increased antitumor cytotoxicity against TNBC and increased production of cytokines such as IL-2 and IFN-γ.
Yang et al., 2023, China [2].	MDA-MB-231 and MDA-MB-468	CAR-T	CD24	Co-culture, flow cytometry, cell proliferation, T cell exhaustion.	The results proved that 24BBz, the CAR-T developed, showed high cytotoxicity against TNBC, based on the production of IL-2 and IFN-γ, high specificity of activation and greater cell proliferation.
Duan et al., 2023, China [24].	4T1 tumor cells	CAR-M	VEGFR2	Co-culture, flow cytometry, phagocytosis and apoptosis.	CAR-Ms had increased expression of MHC-II and CD86 against TNBC cells, as well as pro-inflammatory cytokines (TNF-α and IL-6). The CAR-M type HmC showed greater production of TNF-α, showing greater apoptosis activity and less phagocytosis, suggesting polarization towards the M1 phenotype.
Gammelgaard et al., 2024, Denmark [25].	MDA-MB-231	$CD4^+$ T helper cells (ALECSAT)	-	Co-culture, flow cytometry, cell predictions, cell expansion, TCR clonotype analysis.	ALECSAT AII therapy led to the expansion of T cells and NK cells, increased the proportion of memory T cells in relation to naive T cells, decreased the viability of TNBC cells, and presented a greater TCR repertoire.

CAR: Chimeric Antigen Receptor; CAR-M: Chimeric Antigen Receptor Macrophages; $CD4^+$ T: $CD4^+$ Helper T Cells; $CD8^+$ T Cells: Cytotoxic T Cells; CD24: Cluster of Differentiation 24; DC: Dendritic Cell; EGFR: Epidermal Growth Factor Receptor; miR5119: MicroRNA-5119; PD-1: Programmed Cell Death Protein 1; B7-H3: B7 Family Co-stimulatory Molecule Protein; VEGFR2: Vascular Endothelial Growth Factor Receptor 2; ALECSAT: Adoptive Cellular Therapy with Ex Vivo Stimulated Autologous Peripheral Lymphocytes; BB-trIL2RB-z CAR-T: CAR-T Therapy Targeting B7-H; TCR: T Cell Receptor.

Table 2. *In vivo* studies investigating antitumor effect of cellular immunotherapies in animal models with TNBC.

Study (author, year, and country)	Experimental model	Tumor cell line	Tumor cell volume cell/animal	Cell immunoterapv/ volume cell	Target molecule	Administration/ Frequency	Main fidings
Zhang et al., 2020, China [22].	Female mice model (BALB/c)	4T1 Tumor cell	5×10^5	DC transfected	miRNA 5119	Intravenous 3 doses	Dendritic cells transfected with miR-5119 led to a decrease in tumor growth, an increase in effector T cells positive for IL-2, TNF-α and IFN-γ with greater cytotoxicity. Furthermore, there was a decrease in T cells positive for inhibitory receptors (PD-1, BTLA) and regulatory T cells (Treg), related to immune suppression.
Xia et al., 2020, China [10].	Mice model (SCID)	MDA-MB-231-fluc	1×10^6	CAR-T 2×10^5 - 2×10^6	EGFR	Intravenous 6 doses	CAR-T targeted to EGFR decreased tumor growth, prevented lung metastasis, increased infiltration of tumor T cells, maintaining normal serum levels of pro-inflammatory cytokines (IL-6, IL-1β) and did not present damage to other tissues, in addition to not CAR-T infiltration in normal tissues must be demonstrated.
Zhang et al., 2023, China [23].	Female mice model (NOG)	MDA-MB-231-Luc-4	1×10^6	CAR-T 1×10^6	B7-H3	Intravenous 1 dose	CAR-T targeting B7-H3, called B7-H3BB-trIL2RB-z, delayed tumor growth, increased tumor-infiltrating T cells through increased cell proliferation, increased serum levels of IL-2 and IFN-γ, without presenting toxicity or damage to other organs.
Yang et al., 2023, China [2].	Female mice model (BALB/c)	MDA-MB-231 and MDA-MB-468	3×10^6 1×10^7	CAR-T 1×10^7	CD24	Intravenous and peritumoral 1 dose	CAR-T cells targeting CD24 (24BBz) reduced tumor volume (intravenous and peritumoral), did not change body weight, did not present damage to other organs, achieved greater tumor infiltration of T cells, as well as greater production of GzmB and IFN-γ, which influence the apoptosis of tumor cells. On the other hand, it increased the levels of PD-1, related to the escape of the immune system by tumor cells.
Duan et al., 2023, China [24].	Female mice model (BALB/c)	4T1 tumor cells	5×10^5	CAR-M 1×10^6	VEGFR2	Intravenous 3 doses	HmmC-type CAR-M with TLR4 domain was the most efficient in both normal and immunodeficient mice with a reduction in tumor volume after 3 doses, did not change the weight of the animals and did not damage other organs or local blood vessels.
Gammelgaard et al., 2024, Denmark [25].	Female mice model (NOG)	MDA-MB-231	1×10^6	$CD4^+$ T helper cells (ALECSAT) 1×10^7	-	Intravenous and peritumoral 1 dose	The combination of ALECSAT, an adoptive cell transfer therapy with CD4+ helper T cells, and anti-PDL1 therapy significantly inhibited tumor growth, blocked metastasis, increased activation of pathways associated with the T cell response (IL-2, STAT5, IFN- γ and TNF-α) and prolonged the survival of mice.

CAR: Chimeric Antigen Receptor; CAR-M: Chimeric Antigen Receptor Macrophages; $CD4^+$ T: $CD4^+$ Helper T Cells; CD24: Cluster of Differentiation 24; DC: Dendritic Cell; EGFR: Epidermal Growth Factor Receptor; GzmB: Granzyme B; miR155: MicroRNA-155; TLR4: Toll-Like Receptor 4; Treg: Regulatory T Lymphocytes; PD-1: Programmed Cell Death Protein 1; B7-H3: B7 Family Co-stimulatory Molecule Protein; VEGFR2: Vascular Endothelial Growth Factor Receptor 2; ALECSAT: Adoptive Cellular Therapy with Ex Vivo Stimulated Autologous Peripheral Lymphocytes.

Tumor-associated macrophages (TAMs) can exhibit a phenotype that contributes to cancer progression (M2) by activating anti-inflammatory and immunosuppressive pathways, which can hinder an effective T-cell response, or a phenotype that combats cancer (M1) with a pro-inflammatory profile. Modulating these phenotypes presents a viable alternative for cellular immunotherapy [48–51]. Duan and coauthors [24] developed CAR-M cells targeting VEGFR2, highly expressed in the tumor microenvironment. Intracellular segments of LPS or IFN-γ receptors (TLR4, IFNGR1) were used, alone or in combination, within CAR-M molecules to induce M1 polarization. Among the five types of CAR-M developed (HmA, HmB, HmC, HmD, HmE), HmC, with a simpler structure incorporating the TLR4 intracellular domain, showed the most potent antitumor response. These CAR-M cells demonstrated M1 polarization *in vitro*, enhanced apoptosis, and reduced phagocytosis, likely due to LPS-induced M1 polarization impairing phagocytic capacity [52]. The antitumor action of HmC appeared to be mediated by pro-inflammatory cytokine secretion and apoptosis induction rather than direct phagocytosis of malignant cells.

Since normal cells also express VEGFR2, the activity of CAR-Ms developed against normal VEGFR2-expressing cells was evaluated, revealing no phagocytic activity. CAR-M treatment also inhibited tumor progression in immunocompetent and immunodeficient murine models without organ toxicity, suggesting effective M1 macrophage infiltration specifically targeting cancer cells [53]. Despite promising results, long-term side effects and serum cytokine dosage must be considered, as these were not assessed in the study and may represent limitations.

Dendritic cells (DCs) are highly effective antigen-presenting cells responsible for inducing antitumor responses in T cells [54]. Many cancer treatments observe T-cell exhaustion, characterized by inhibitory receptor expression and reduced effector cytokine release, contributing to tumor progression [55,56]. In this context, dendritic cell therapies can induce and enhance T-cell-mediated immune responses [57]. However, DC vaccines may induce inhibitory ligands like PD-L1, limiting immunotherapy, while miRNAs emerge as an alternative for modulating these cells [58,59].

Zhang and coauthors [22] analyzed the efficacy of miR-5119, which can regulate multiple factors suppressing antitumor immunity, including PD-L1, as a potential restorer of exhausted $CD8^+$ T cells. *In vitro*, miR-5119-transfected DCs increased cytokine production (IL-2, TNF-α, IFN-γ), indicating significant immunological recovery.

In vivo studies demonstrated enhanced antitumor response, reduced tumor growth, increased effector cytokine production, and greater $CD8^+$ T-cell cytotoxicity in mice treated with miR-5119-engineered DC vaccines. These treatments also downregulated Tregs ($CD4^+$ $CD25^+$ $Foxp3^+$) and reduced T-cell exhaustion markers such as PD-1, TIM-3, and BTLA, highlighting a comprehensive antitumor response [60]. Previous studies on DC-based immunotherapy for melanoma and non-small cell lung cancer reported similar challenges with tumor-induced immunosuppression, which miR-5119 modulation may help overcome [61–64].

Gammelgaard and coauthors studied Adoptive Cell Therapy (ACT), which is increasingly being explored and selected as a treatment method for various cancers. It has shown potential as an effective option for solid tumors like TNBC [25]. This study developed ACT cells from blood cells, involving the proliferation of $CD4^+$ helper T cells, which were modified and used to selectively expand lymphocytes capable of recognizing and responding to reactivated antigens [66]. The ALECSAT therapy used *in vitro* led to increased NK and memory T cells, synergistically enhancing cytotoxicity against tumor cells [67,68]. *In vivo*, the therapy increased PD-L1 expression, necessitating combination with anti-PD-L therapy. This method inhibited tumor growth, blocked metastasis, and activated T-cell-related pathways. Another study involving various types of breast cancer indicated that combining immunotherapy with autologous dendritic cells and chemotherapy with doxorubicin and cyclophosphamide (NAC-AC) was beneficial for patients, increasing T cells in peripheral blood [69].

The use of cells in cancer treatment requires further exploration, and human studies should be encouraged to verify its effects. Additionally, as current studies often observe immediate outcomes, long-term analyses simulating human treatments are needed. The therapies discussed in this review are promising and hold potential as alternative treatments for this aggressive and heterogeneous breast cancer subtype.

CONCLUSION

The review highlights the promising potential of cellular immunotherapies such as CAR-T B7-H3, CAR-T EGFR, CAR-T CD24, miR5119-transfected dendritic cells, CAR-M, and autologous $CD4^+$ T lymphocytes. These therapies demonstrated significant effects in the analyses performed, with autologous $CD4^+$ T lymphocyte immunotherapy achieving the greatest reduction in triple-negative breast cancer. Our review provides a valuable foundation for the development of TNBC therapies using immune cells. Future studies are needed to verify the effectiveness of these therapies in humans.

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Conceptualization, J.A.D.S., G.P.R., Y.V.B., L.A.D.A. and P.P.C.; Methodology, J.A.D.S., G.P.R., Y.V.B. and E.N.S.; Validation, J.A.D.S., G.P.R., Y.V.B., L.A.D.A. and P.P.C.; Formal analysis, J.A.D.S., G.P.R., Y.V.B., E.N.S., L.A.D.A. and P.P.C.; Investigation, J.A.D.S., G.P.R., Y.V.B., E.N.S., L.A.D.A. and P.P.C.; Resources, L.A.D.A. and P.P.C.; Data curation, J.A.D.S., G.P.R., Y.V.B., E.N.S., L.A.D.A. and P.P.C.; Writing—original draft preparation, J.A.D.S., G.P.R., Y.V.B., L.A.D.A. and P.P.C.; Writing—review and editing, E.N.S. and P.P.C; Visualization, L.A.D.A. and P.P.C.; Supervision, L.A.D.A. and P.P.C.; Project administration, P.P.C.; Funding acquisition, L.A.D.A. and P.P.C.; These authors contributed equally to this work and share first authorship: J.A.D.S., G.P.R. and Y.V.B.

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Supplementary Material: Table S1. Detailed search strategy for applying filters in the PubMed/Medline and Scopus databases. Table S2. Bias and quality analysis using the SYRCLE method of *in vivo* studies included in the systematic review. – https://github.com/labiomol/Santos_et_al_supplementary_material/

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