Article published online: 2024-09-13

Therapeutic Vaccination Strategies for Breast Cancer

Therapeutische Vakzinierungsstrategien beim Mammakarzinom

OPEN ACCESS

Authors

Christian M. Tegeler[1, 2], Andreas D. Hartkopf[1], Juliane S. Walz[2, 3, 4, 5]

Affiliations

1 Department für Frauengesundheit, Universitätsklinikum Tübingen, Tübingen, Deutschland
2 Abteilung für Peptid-basierte Immuntherapie, Institut für Immunologie, Universitätsklinikum Tübingen, Tübingen, Deutschland
3 Klinische Kooperationseinheit (KKE) – Translationale Immunologie, Deutsches Konsortium für Translationale Krebsforschung (DKTK), Department für Innere Medizin, Universitätsklinikum Tübingen, Tübingen, Deutschland
4 Cluster of Excellence iFIT (EXC2180) "Image-Guided and Functionally Instructed Tumor Therapies, Universität Tübingen, Tübingen, Deutschland
5 Deutsches Konsortium für Translationale Krebsforschung (DKTK) und Deutsches Krebsforschungszentrum (DKFZ), Standort Tübingen, Tübingen, Deutschland

Keywords

Breast Cancer, Therapy, Vaccination

Schlüsselwörter

Mammakarzinom, Therapie, Vakzinierung

Bibliography

Senologie 2024; 21: 204–207

DOI 10.1055/a-2256-4215

ISSN 1611-6453

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. med. Christian M. Tegeler
Department für Frauengesundheit, Universitätsklinikum Tübingen, Calwerstraße 7, 72076 Tübingen, Deutschland
christian.tegeler@med.uni-tuebingen.de

Deutsche Version unter: https://doi.org/10.1055/a-2256-4215.

ABSTRACT

Even though the impact of the immune system on the clinical course of cancer has been known for decades, its role in the treatment of various tumor entities has often been given little consideration. In recent years, the treatment landscape for breast cancer has undergone significant changes. Routine treatment has been revolutionized, in particular, by the use of T cell-based immunotherapies in the form of immune checkpoint inhibitors (ICIs). While this underscores the importance of the immune system in the treatment of breast cancer, other T cell-based immunotherapies, such as therapeutic vaccines, do still not play a significant role in clinical practice. In recent years, numerous studies on various vaccine candidates have been conducted, some of which have demonstrated a successful induction of an immune response. The selection of antigens and routes of administration/adjuvants capable of inducing long-lasting and clinically effective T cell responses remains a key challenge. The combination of ICIs with therapeutic vaccines could also hold promise for the future, by enhancing the specificity of the T cell response and thus augmenting the anti-tumor effect.

ZUSAMMENFASSUNG

Der Einfluss des Immunsystems auf den Verlauf einer Krebserkrankung ist seit Jahrzehnten bekannt, trotzdem wurde ihm in der Behandlung diverser Tumorentitäten aber oft wenig Stellenwert beigemessen. In den letzten Jahren hat sich die Therapielandschaft des Mammakarzinoms deutlich verändert. Besonders der Einsatz von T-Zell-basierten Immuntherapien in Form von Immun-Checkpoint-Inhibitoren (ICI) hat die Routinebehandlung revolutioniert. Obwohl dies die Bedeutung des Immunsystems in der Behandlung des Mammakarzinoms unterstreicht, spielen weitere T-Zell-basierte Immuntherapien, wie beispielsweise therapeutische Impfstoffe, bislang keine relevante klinische Rolle. In den letzten Jahren gab es zahlreiche Studien zu verschiedenen Impfstoffkandidaten, die teilweise auch Erfolge in der Induktion einer Immunantwort zeigen konnten. Eine zentrale Herausforderung stellt weiterhin die Auswahl geeigneter Antigene und Applikationsformen/Adjuvantien zur Induktion lang anhaltender und klinisch effektiver T-Zell-Antworten dar. Vielversprechend könnte in Zukunft auch die Kombination von ICI mit Vakzinen sein, um die Spezifität der T-Zellantwort und damit die Anti-Tumorwirkung zu erhöhen.

The role of the immune system is to monitor cells in the body and to recognize and eliminate abnormal cells at an early stage. Many of the immunotherapies developed in recent years are based on immune recognition of tumor cells. In the case of breast cancer, the adoption of T cell-based immunotherapies, especially treatment with immune checkpoint inhibitors (ICIs), into routine clinical practice in the metastatic and neoadjuvant settings is of particular importance [1, 2]. Yet currently only a small proportion of patients benefit from this therapy [3], and there is a great need for additional immunotherapeutic approaches that improve the specificity of the immune response and increase the response rates. Therapeutic vaccination, an approach where the immune system is specifically directed against tumor cells, is one way of achieving this goal. Unlike vaccinations against pathogens, which have proven to be highly successful in the prevention of previously fatal infectious diseases, cancer vaccines are used only in the therapeutic setting where T cells are trained to specifically target antigens presented on tumor cells via human leukocyte antigens (HLA). While numerous vaccine candidates for breast cancer treatment are currently being evaluated in clinical trials, this therapeutic approach has not yet been adopted in routine clinical practice.

Cancer-specific peptides as the primary vaccination target

The selection of suitable antigens, which should be specific for the tumor and occur at a high rate in many patients, is a key prerequisite for the development of cancer vaccines. Peptides, presented on the cell surface via HLA molecules, are the target of T cell-mediated immune response. Since tumor cells differ in these peptides from healthy cells, the immune system is able to recognize tumor peptides as foreign and destroy them. Potentially useful tumor antigens include, on the one hand, neo-epitopes which originate from tumor-specific mutations and have been described as the key target structure of ICI-mediated immune response, and, on the other hand, tumor-associated antigens (TAAs) which are exclusively presented in tumor tissue as the result of changes in gene expression or processing [4, 5, 6, 7]. Regardless of their origin and presentation, tumor-exclusive peptides, ideally presented by the majority of patients, are optimal candidates for therapeutic vaccination as they allow widespread use in clinical practice. Breast cancer research into TAAs focuses on the epidermal growth factor receptor 2 (HER2) as a target which has been investigated in numerous studies. In addition, other antigens for cancer vaccines, including human epidermal growth factor receptor 3, folate receptor α and programmed cell death ligand-1, have been described; these are also currently being evaluated in clinical trials [8, 9]].

Treatment setting

Various strategies for the application of these antigens, in combination with suitable adjuvants, are available, including peptide vaccines, DNA- or RNA-based vaccines as well as approaches based on dendritic cells or viral vectors. In the case of DNA- or RNA-based vaccines, cancer antigen-coding DNA or RNA is introduced into the body. The recipient's cells take it up and start producing antigens, which are then recognized as foreign by the immune system [10, 11]. This principle is also utilized in the case of viral vectors, which introduce the genetic information into the body as a vehicle and then trigger an immune response to the antigens produced [12]. With peptide-based vaccines, the cancer antigens are applied directly in the form of short sequences of amino acids. The peptides are produced synthetically and administered in combination with adjuvants that stimulate the immune system [13]. Cell-based approaches use the patient's own dendritic cells which are ex vivo loaded with tumor antigens and then infused back into the patient. Next, the loaded dendritic cells present the tumor antigens to T cells [14]. In addition to the selection of optimal tumor antigens, adjuvants and application strategies as well as the timing of administration of the cancer vaccine is critical for its success. An optimum ratio of effector cells to target cells is crucial for the effectiveness of the treatment, i. e. the number of functional T cells available must be sufficient to eliminate the existing tumor cells. With breast cancer, this would, for example, be the case postoperatively, with or without prior neoadjuvant chemotherapy (NACT). Vaccine treatment could be administered either alone or in combination with another treatment which does not have a negative effect on the functioning of the immune system (e. g. ICI treatment). In addition to this "classical setting", newer concepts also evaluate the effectiveness of its use as an adjunct treatment to NACT.

Current state of clinical trials

Therapeutic vaccines to treat breast cancer have been evaluated for many years [15]. The first targets identified were tumor antigens from HER2 in patients with HER2-positive breast cancer. Initial successes were achieved early on with the induction of an immune response in HLA-A2-positive patients [16, 17, 18]. Today, further tumor antigens are investigated; however, the range of suitable targets is more limited in breast cancer compared to other tumor entities, since most of the antigens that have been studied were not pursued further due to a lack of or insufficient immune responses [8]. Only a small proportion of the cancer vaccines developed could be taken to more advanced stages of clinical development. HER2 is still the primary target. The current phase II/III studies (▶ **Table 1**) have already shown promising immune responses in early phases of the clinical development. Here, again, the increasing impact of well-established immunotherapies is obvious. The number of studies evaluating ICIs in combination with therapeutic cancer vaccines continue to increase. One example is the NSABP FB-14 study, which showed already years ago that the peptide-based vaccine was able to induce HER2-related immunogenicity [17]; this therapeutic vaccine is now being evaluated in combination with an ICI in triple-negative metastatic breast cancer (NCT04024800). The largest study in German-speaking countries is the Flamingo-01 trial, evaluating a promising peptide-based vaccine targeting HER2 in combination with the granulocyte-macrophage colony stimulating factor

▶ **Table 1** Summary of ongoing phase II/III studies on therapeutic vaccination in patients with breast cancer. Data according to https://clinicaltrials.gov/.

Trial identifier	Phase	Principle of action	Setting	Cohort	Target structure
NCT05232916	III	Peptide-based + GM-CSF	eBC	HER2 + BC with non-pCR after NACT or high recurrence risk after NACT	HER2
NCT03562637	III	Peptide-based	eBC	Globo H-positive TNBC	Globo H
NCT03384914	II	DC-based vs. DNA-based	eBC	HER2 + BC with non-pCR after NACT	HER2
NCT04329065	II	DNA-based + THP	eBC	HR-/HER2 + BC before surgery	HER2
NCT04197687	II	Peptide-based + GM-CSF	eBC	HER2 + BC with non-pCR after NACT	HER2
NCT03012100	II	Peptide-based + GM-CSF + cyclophosphamide	eBC	TNBC	FOLR1
NCT03804944	II	Letrozole + radiation vs. letrozole + radiation + peptide-based vs. letrozole + radiation + ICI vs. letrozole + radiation + peptide-based + ICI	eBC	HR+/HER2- BC, locally advanced before surgery	Ftl-3
NCT03632941	II	Alphavirus-based + ICI	mBC	HR-/HER2 + BC	HER2
NCT04348747	II	DC-based + ICI	mBC	TNBC or HER2 + BC with brain metastases	HER2/HER3
NCT03328026	II	Allogeneic BC cells + ICI + cyclophosphamide	mBC	All subtypes	GM-CSF PD-L1 IDO
NCT02491697	II	DC-based + Capecitabine	mBC	All subtypes	CIK agonist
NCT04024800	II	Peptide-based + ICI	mBC	TNBC	HER2
NCT04348747	II	DC-based + ICI	mBC	TNBC/HER2 + BC	HER2/HER3
NCT03606967	II	Peptide-based + nab-paclitaxel + 2 ICI	mBC	TNBC	Personalized vaccine
NCT03761914	II	Peptide-based + ICI	mBC	TNBC	WT1

Abbreviations: GM-CSF: granulocyte-macrophage colony stimulating factor; DC: dendritic cell; DNA: deoxyribonucleic acid; vs.: versus; THP: neoadjuvant chemotherapy with THP: neoadjuvant chemotherapy with Taxol (Paclitaxel), Herceptin (trastuzumab) and Perjeta (pertuzumab); ICI: immune checkpoint inhibitor; BC: breast cancer: eBC: early breast cancer; mBC: metastatic breast cancer; nab-paclitaxel: nanoparticle albumin-bound paclitaxel; HER2: human epidermal growth factor receptor 2; non-pCR: histological evidence of residual tumor cells after surgery; NACT: neoadjuvant chemotherapy; TNBC: triple-negative breast cancer; HR+ BC: hormone receptor-positive breast cancer, HR- BC: hormone receptor-negative breast cancer; Globo H: globohexaosyl-ceramide; FOLR1: folate receptor α; ftl-3: FMS-like tyrosine kinase 3; HER3: human epidermal growth factor receptor 3; PD-L1: Programmed cell death ligand-1; IDO: indolamine-2,3-dioxygenase: CIK agonist: cytokine-induced killer agonist; WT1: Wilms' tumor 1 protein

(GM-CSF) in patients after neoadjuvant chemotherapy (NACT) and at high risk of recurrence (NCT05232916). Of particular note are also newer concepts, investigating the use of additive preoperative vaccination. The vaccination is administered for example in combination with neoadjuvant chemotherapy and HER2-targeted therapy (NCT04329065), an approach that aims at improving the response rate through vaccination. Another interesting concept is offered by the CBCV trial (NCT03804944), in which the preoperative administration of letrozole in patients with hormone receptor-positive/HER2-negative breast cancer is extended by a 4-arm concept with local radiation, either without additional therapy or in combination with peptide-based vaccination, ICIs or a combination thereof; the histological response is evaluated after completion of treatment.

Conclusion

For the first time, numerous therapeutic vaccination strategies for breast cancer, which have already shown an adequate immune response in earlier studies, are currently evaluated in advanced study phases. In addition to the classical adjuvant setting, new concepts are emerging that either use ICI as a combination partner or aim to improve the response rate in patients undergoing NACT. The complexity and costs of these personalized approaches remain a hurdle to establishing them in clinical practice. In addition, there is still a lack of suitable breast cancer antigens that could be used for off-the-shelf approaches in large patient populations.

Implications for clinical practice

Therapeutic vaccines do not play a role in breast cancer therapy in today's routine clinical practice. However, the successes achieved with ICI treatment underscore the potential of the immune system to control breast cancer, even in cases with poor prognosis. Nevertheless, there is still room for improvement, as ICIs cannot (yet) be used in all patients with breast cancer and are only effective in a subgroup of patients. Cancer vaccines provide the opportunity to improve the specificity of the immune responses, thereby optimizing the effectiveness of immunotherapies. Going forward, therapeutic vaccination strategies (possibly in combination with an ICI, depending on the subtype) could be a useful addition to breast cancer therapy to further improve treatment options, in particular in cases where therapeutic alternatives are limited, for example in the case of histological evidence of residual tumor after NACT.

Conflict of Interest

C.M.T. declares that there are no competing interests. A.D.H. declares travel support from AstraZeneca, Lilly and MSD and honorary positions with AstraZeneca, Lilly and MSD. J.S.W. discloses consultancy work with Swarm Oncology, Laboratories Delbert and OrganoidScience. J.S.W. is a shareholder in ViferaXS GmbH.

References

[1] Cortes J, Rugo HS, Cescon DW et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. N Engl J Med 2022; 387 (3): 217–226. doi:10.1056/NEJMoa2202809

[2] Schmid P, Cortes J, Pusztai L et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020; 382 (9): 810–821. doi:10.1056/NEJMoa1910549

[3] Baxi S, Yang A, Gennarelli RL et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. Bmj 2018; 360: k793. doi:10.1136/bmj.k793

[4] Morisaki T, Kubo M, Umebayashi M et al. Neoantigens elicit T cell responses in breast cancer. Sci Rep 2021; 11 (1): 13590. doi:10.1038/s41598-021-91358-1

[5] Chabanon RM, Pedrero M, Lefebvre C et al. Mutational Landscape and Sensitivity to Immune Checkpoint Blockers. Clin Cancer Res 2016; 22 (17): 4309–4321. doi:10.1158/1078-0432.CCR-16-0903

[6] Schuster H, Peper JK, Bösmüller HC et al. The immunopeptidomic landscape of ovarian carcinomas. Proc Natl Acad Sci U S A 2017; 114 (46): E9942–e9951. doi:10.1073/pnas.1707658114

[7] Walz S, Stickel JS, Kowalewski DJ et al. The antigenic landscape of multiple myeloma: mass spectrometry (re)defines targets for T-cell-based immunotherapy. Blood 2015; 126 (10): 1203–1213. doi:10.1182/blood-2015-04-640532

[8] Zhu SY, Yu KD. Breast Cancer Vaccines: Disappointing or Promising? Front Immunol 2022; 13: 828386. doi:10.3389/fimmu.2022.828386

[9] Corti C, Giachetti P, Eggermont AMM et al. Therapeutic vaccines for breast cancer: Has the time finally come? Eur J Cancer 2022; 160: 150–174. doi:10.1016/j.ejca.2021.10.027

[10] Vishweshwaraiah YL, Dokholyan NV. mRNA vaccines for cancer immunotherapy. Front Immunol 2022; 13: 1029069. doi:10.3389/fimmu.2022.1029069

[11] Paston SJ, Brentville VA, Symonds P et al. Cancer Vaccines, Adjuvants, and Delivery Systems. Front Immunol 2021; 12: 627932. doi:10.3389/fimmu.2021.627932

[12] McCann N, O'Connor D, Lambe T et al. Viral vector vaccines. Curr Opin Immunol 2022; 77: 102210. doi:10.1016/j.coi.2022.102210

[13] Nelde A, Rammensee HG, Walz JS. The Peptide Vaccine of the Future. Mol Cell Proteomics 2021; 20: 100022. doi:10.1074/mcp.R120.002309

[14] Perez CR, De Palma M. Engineering dendritic cell vaccines to improve cancer immunotherapy. Nat Commun 2019; 10 (1): 5408. doi:10.1038/s41467-019-13368-y

[15] Curigliano G, Spitaleri G, Pietri E et al. Breast cancer vaccines: a clinical reality or fairy tale? Ann Oncol 2006; 17 (5): 750–762. doi:10.1093/annonc/mdj083

[16] Peoples GE, Gurney JM, Hueman MT et al. Clinical trial results of a HER2/neu (E75) vaccine to prevent recurrence in high-risk breast cancer patients. J Clin Oncol 2005; 23 (30): 7536–7545. doi:10.1200/JCO.2005.03.047

[17] Holmes JP, Benavides LC, Gates JD et al. Results of the first phase I clinical trial of the novel II-key hybrid preventive HER-2/neu peptide (AE37) vaccine. J Clin Oncol 2008; 26 (20): 3426–3433. doi:10.1200/JCO.2007.15.7842

[18] Mittendorf EA, Storrer CE, Foley RJ et al. Evaluation of the HER2/neu-derived peptide GP2 for use in a peptide-based breast cancer vaccine trial. Cancer 2006; 106 (11): 2309–2317. doi:10.1002/cncr.21849