

Cancer Vaccines

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses cancer vaccines.

1. Experimental, Investigational, or Unproven

Aetna considers the following cancer vaccines experimental, investigational, or unproven because the safety and effectiveness of these approaches has not been established:

1. Helper multi-peptide (6MHP) vaccine for metastatic melanoma
2. HLA-A24-binding peptide vaccines for gastric cancer
3. Melanoma vaccine (also known as Theraccine vaccine or Oncophage vaccine) for any indication
4. p16(INK4a)-based peptide vaccine for human papillomavirus-associated cancers (e.g., anal, cervical, oropharyngeal, penile, rectal, vaginal, and vulvar cancers)
5. p62 DNA vaccine (Elenagen) for solid tumors (e.g., breast, kidney, lung, and ovary cancers as well as melanoma)
6. Use of whole cancer stem cell-based vaccines as an adjuvant strategy for the surgical management of solid tumors
7. Vaccine therapy including tumor-associated antigenic peptide-based vaccines in the treatment of the following cancers (not an all-inclusive list) because the clinical evidence is not sufficient to permit conclusions on the health outcome effects of vaccine therapy in the treatment of these cancers:

1. Acute myeloid leukemia
2. Breast cancer
3. Central nervous system cancers (e.g., glioblastoma and neuroblastoma)
4. Colorectal cancer
5. Gallbladder cancer
6. Gastric cancer
7. Glioma
8. Head and neck cancer
9. Hepatic cancer
10. Lung cancer
11. Oral squamous cell carcinoma
12. Ovarian cancer
13. Pancreatic cancer.

CPT Codes / HCPCS Codes / ICD-10 Codes

There is no specific CPT code for melanoma vaccine (e.g., Theraccine vaccine or Oncophage vaccine, cancer vaccine therapy, helper multi-peptide (6MHP) vaccine, or vaccine therapy including tumor-associated antigenic peptide-based vaccines):

Code

Code Description

CPT codes not covered for indications listed in the CPB:

HLA-hyphenA-hyphen24-hyphenbinding peptide vaccines, p16(INK4a)-hyphenbased peptide vaccine, p62 DNA vaccine (Elenagen), Stem cell-hyphenbased vaccines - no specific code:

ICD-10 codes not covered for indications listed in the CPB:

Melanoma of ovary or kidney - no specific code :

C00.0 – C96.9	Malignant neoplasms
D00.00 - D09.9	Carcinoma in situ
Z23	Encounter for immunization

Background

Melanoma Vaccine

Melanoma vaccine is prepared from melanoma cell lines that are cultured in-vitro. The vaccine product is designed to contain 1 or more antigens that are unique to melanoma cells; some preparations also contain "adjuvants" (such as bacillus Calmette-Guerin [BCG]) thought to enhance immunogenicity of the preparation.

Currently, no melanoma vaccine products are licensed for marketing in the United States. Until a commercial preparation is available, there is significant potential for variability between products and batches. Effects that are seen in patients to whom these products are administered may be due to the components thought to be active, or to other components which are contaminants, adjuvants or excipients. In those studies lacking a concurrent control group, it is impossible to distinguish which components are active. Ribic Immunochem Research has developed a standardized melanoma vaccine called Melacine. As a biological, this product would be evaluated and licensed by the Center for Biological Evaluation and Research of the Food and Drug Administration (FDA). At this time, no application for licensure has been filed for this product.

Several published studies have suggested that melanoma vaccine may be effective in the treatment of malignant melanoma and/or prevention of metastasis of melanoma; however, these studies are not adequate to establish the safety and/or efficacy of this therapy. In addition, there have been a number of reports of phase I and phase II studies that have demonstrated increases in tumor-specific cytotoxic T lymphocytes and other immune responses in patients vaccinated with various melanoma vaccines. A number of these studies have incorporated interleukin-2 and other adjuvants to improve immune response to melanoma vaccine. The second interim report from a phase III, multi-center randomized controlled clinical trial of a melanoma vaccine, however, showed no significant overall survival benefit in vaccinated melanoma patients. A retrospective analysis of clinical trial results identified subsets of patients that appeared to have improved survival with the vaccine; this retrospective analysis suggests that a vaccine may be effective in selected subgroups of melanoma patients.

Randomized controlled clinical trials, where subgroups of patients are identified prospectively, are necessary to confirm the efficacy of melanoma vaccine in selected patient subgroups. Kuhn and Hanke (1997) concluded in a recent review of the current status of melanoma vaccines that "[t]he clinical effectiveness of melanoma vaccines is unclear and adequately controlled studies need yet to be performed". A former President of the American Cancer Society stated that "[t]he success of melanoma vaccines has been inhibited by the large number of potential antigen targets on the melanoma cell, which may vary from tumor to tumor. In addition, the lack of intermediate end points for assessment of the effect of immunotherapy has impeded research in this field."

The FDA has deemed the Antigenics Inc. (New York, NY) Oncophage late-stage investigational cancer vaccine an orphan drug for metastatic melanoma. The FDA orphan drug designation was designed to encourage the development of therapies for conditions affecting fewer than 200,000 people in the United States. The designation entitles the sponsor to aid with the development program, tax breaks, waivers from certain regulatory fees and 7 years of additional marketing exclusivity if the product eventually is approved.

The Oncophage vaccine is prepared by removing a tumor from the patient and isolate specific antigens of the particular cancer. The vaccine is composed of heat-shock proteins that are bound to other proteins specific to tumor antigens. According to Antigenics, Inc., studies have shown that the protein complex, when purified from tumor cells and reintroduced to the patient, appears to stimulate cellular immunity. The immune response appears to be directed specifically to cancer cells, leaving the patient's healthy tissue intact. In May 2002, Antigenics reported that it had begun enrolling patients in the United States and Europe in a pivotal phase III trial of Oncophage for stage IV metastatic melanoma.

Elliott and Dalglish (2004) stated that melanoma vaccines offer new hope to patients with metastatic melanoma, although convincing survival advantages have yet to be reported. Bystryn and Reynolds (2005) stated that vaccines are a promising but still experimental treatment for melanoma.

Guidelines on malignant melanoma from the National Institute for Health and Clinical Excellence (2006) have concluded that "[v]accine therapy for advanced [malignant melanoma] remains uncertain and its use should only be in the context of a clinical trial." A systematic evidence review in BMJ Clinical Evidence (Savage, 2006) concluded that adjuvant vaccines in people with malignant melanoma are of "unknown effectiveness."

Lens and colleagues (2008) assessed different vaccines tested in stage III and/or IV melanoma patients. Systematic review of the published evidence on vaccine therapy in melanoma was carried out. Melanoma vaccines can be classified into 6 groups:

1. whole-cell vaccines,
2. dendritic cell vaccines,
3. peptide vaccines,
4. ganglioside vaccines,
5. DNA vaccines and
6. viral vectors.

The main characteristics of these vaccines including their advantages and disadvantages and the results from conducted trials were presented. Clinical responses to melanoma vaccines are still poor and currently there is no melanoma vaccine with a proven efficacy. The authors concluded that vaccine therapy still remains an experimental therapy in patients with metastatic melanoma. Further research is needed although a future therapy for advanced melanoma is probably a multi-modal approach including vaccines, adjuvants and negative co-stimulatory blockade. This is in agreement with the observations of Stein and Brownell (2008) who noted that advanced melanoma has a poor prognosis, and standard adjuvant treatment offers little survival advantage. Current efforts are aimed at combining chemotherapy and novel immunomodulators, which include vaccines, cytokines, and anti-CTLA4 antibodies. Hundreds of combination therapies are currently undergoing clinical trials. All advanced melanoma patients should be considered for enrollment in a trial for their own benefit as well as for the advancement of melanoma treatment. Thus far, no single investigative approach stands out as highly effective, however, they all hold promise with rare patients showing durable responses. Most treatment protocols are evaluating combinations of adjuvant therapies, hoping to achieve a synergistic effect.

Lesterhuis and associates (2008) stated that dendritic cells are the directors of the immune system, capable of inducing tumor antigen-specific T-cell and B-cell responses. As such, they are currently applied in clinical studies in cancer patients. Early small clinical trials showed promising results, with frequent induction of anti-cancer immune reactivity and clinical responses. In recent years, additional trials have been carried out in melanoma patients, and although immunological responses are often reported, objective clinical responses remain anecdotal with objective response rates not exceeding 5 to 10 %. Thus, dendritic cells vaccination research has now entered a stage in between "proof of principle" and "proof of efficacy" trials. Crucial questions to answer at this moment are why the clinical responses remain scarce and what can be done to improve the efficacy of vaccination.

Faries et al (2009) examined the effect of the addition of granulocyte/macrophage colony-stimulating factor (GM-CSF) to vaccination with a melanoma vaccine. A total of 97 patients with resected melanoma (stage II-IV) were enrolled, stratified by stage, and randomized to receive a cellular melanoma vaccine with or without GM-CSF. The primary endpoint was delayed-type hypersensitivity (DTH) response to melanoma cells. Antibody responses, peripheral leukocyte counts, and survival were also examined. The GM-CSF arm showed enhanced antibody responses with an increase in IgM titer against the TA90 antigen and increased TA90 immune complexes. This arm also had diminished anti-melanoma cell delayed-type hypersensitivity response. Peripheral blood leukocyte profiles showed increases in eosinophils and basophils with decreased monocytes in the GM-CSF arm. These immune changes were accompanied by an increase in early melanoma deaths and a trend toward worse survival with GM-CSF. The authors concluded that these findings suggested that GM-CSF is not helpful as an immune adjuvant in this dose and schedule and raised concern that it may be harmful. Based on the discordant findings of an immune endpoint and clinical outcome, the use of such surrogate endpoints in selecting treatments for further evaluation must be done with a great deal of caution.

In a phase II, multi-center, randomized trial, Slingluff et al (2009) examined whether local administration of GM-CSF augments immunogenicity of a multi-peptide vaccine. It also assessed immunogenicity of administration in 1 versus 2 vaccine sites. A total of 121 eligible patients with resected stage IIB to IV melanoma were vaccinated with 12 major histocompatibility complex class I-restricted melanoma peptides to stimulate CD8+ T cells plus a human leukocyte antigen (HLA)-DR-restricted tetanus helper peptide to stimulate CD4+ T cells, emulsified in incomplete Freund's adjuvant, with or without 110 microg GM-CSF. Among 119 evaluable patients, T-cell responses were assessed by IFN-gamma ELISPOT assay and tetramer analysis. Clinical outcomes were recorded. CD8+ T-cell response rates to the 12 MHC class I-restricted melanoma peptides (by day 50) with or without GM-CSF were 34 % and 73 %, respectively ($p < 0.001$), by direct ELISPOT assay. Tetramer analyses corroborated the functional data. CD4+ T-cell responses to tetanus helper peptide were higher without GM-CSF (95 % versus 77 %; $p = 0.005$). There was no significant difference by number of vaccine sites. Three-year overall and disease-free survival estimates (95 % confidence interval) were 76 % (67 % to 83 %) and 52 % (43 % to 61 %), respectively, with too few events to assess differences by study

group. The authors concluded that high immune response rates for this multi-peptide vaccine were achieved, but CD8+ and CD4+ T-cell responses were lower when administered with GM-CSF. These data challenge the value of local GM-CSF as a vaccine adjuvant in humans.

Kaufman (2012) noted that the inherent immunogenicity of melanoma and renal cell carcinoma (RCC) has made these tumors a focus of considerable research in vaccine development. Recent data from murine studies of immuno-surveillance have highlighted the importance of both innate and adaptive immune responses in shaping a tumor's inherent susceptibility to immune surveillance and immunotherapy. Melanoma has been a useful model for the identification of tumor-associated antigens and a number of putative renal cell antigens have been described more recently. These antigens have been targeted using a variety of vaccine strategies, including protein- and peptide-based vaccines, recombinant antigen-expressing vectors, and whole cell vaccine approaches. While evidence for clinical benefit has been disappointing to date, several current phase III clinical trials are in progress based on promising results from phase II studies. Accumulating data suggest that the tumor microenvironment and mechanisms of immunological escape by established tumors are significant barriers that must be overcome before vaccine therapy can be fully realized. The author discussed the basis for vaccine development, described some of the more promising vaccine strategies in development, and mentioned some of the tumor escape mechanisms that block effective anti-tumor immunity for melanoma and RCC. The author listed 4 phase III clinical trials in melanoma vaccine (1 completed, and 3 in progress).

Ovarian Cancer Vaccine

Ovarian cancer is cancer that begins in the ovaries. In general, ovarian tumors are named according to the kind of cells the tumor started from and whether the tumor is benign or cancerous. There are 3 main types of ovarian tumors:

1. germ cell tumors start from the cells that produce the ova (eggs);
2. stromal tumors start from connective tissue cells that hold the ovary together and produce the female hormones estrogen and progesterone;
3. epithelial tumors start from the cells that cover the outer surface of the ovary.

Therapeutic vaccines are intended to coerce the cellular components of the immune system to attack malignant tissue. Prophylactic vaccines are intended to induce the production of antibodies capable of neutralizing viral antigens before they infect host cells.

The National Cancer Institute Ovarian Epithelial Cancer Treatment PDQ (2008) states that vaccines are under clinical evaluation in the treatment of ovarian cancer, primarily as part of consolidation therapy.

According to a 2010 Cochrane database review, prognosis of ovarian cancer remains poor despite advances in chemotherapy. Antigen-specific active immunotherapy aims to induce a tumor-antigen-specific anti-tumor immune responses as an alternative treatment for ovarian cancer. The objective of this study was to assess feasibility of antigen-specific active immunotherapy for ovarian cancer. A systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2009, Cochrane Gynaecological Cancer Group Specialized Register, MEDLINE and EMBASE databases and clinicaltrials.gov was performed (1966 to July 2009). Randomized controlled trials, as well as non-randomized non-controlled studies that included patients with epithelial ovarian cancer, irrespective of stage of disease, and treated with antigen-specific active immunotherapy, irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, schedule, and reported clinical or immunological outcomes. Thirty-six studies were included. Response definitions showed substantial variation between trials, which makes comparison of trial results unreliable. Information on adverse events was frequently limited. However, three large randomised placebo-controlled trials did not show any clinical benefit despite induction of immune responses in approximately 60% of patients. Other small studies targeting many different tumour antigens showed promising immunological results. As these strategies have not yet been tested in randomized controlled trials (RCTs), no reliable inferences about clinical efficacy can be made. Given the promising immunological results, limited side effects and toxicity exploration of clinical efficacy in large well-designed RCTs may be worthwhile. It was concluded that despite promising immunological responses no clinically effective antigen-specific active immunotherapy is yet available for ovarian cancer. Furthermore, the adoption of guidelines to ensure uniformity in trial conduct, response definitions and trial reporting is recommended to improve quality and comparability of immunotherapy trials.

In a review, Gardner and Jewell (2011) wrote that future trials will determine the role of biologic agents and vaccine therapies for ovarian cancer, as well as their impact on quality of life.

Vaccines for Selected Types of Cancer

Krishnadas et al (2013) stated that patients with relapsed stage 4 neuroblastoma have an extremely poor long-term prognosis, making the investigation of new agents of interest. These investigators reported the outcome of the first patient treated in a phase I study for relapsed neuroblastoma, using the chemotherapy agent decitabine to up-regulate cancer testis antigen expression, followed by a dendritic cell vaccine targeting the cancer testis antigens MAGE-A1, MAGE-A3, and NY-ESO-1. The patient in this study had persistent tumor in his bone marrow after completion of standard therapy for neuroblastoma, including multi-agent chemotherapy, tumor resection, stem cell transplantation, radiation therapy, and anti-GD2 monoclonal antibodies. His marrow disease persisted despite chemotherapy, which was given while the vaccine was being produced. After 3 cycles of

decitabine and vaccine, this patient achieved a complete remission and is now 1 year from his last treatment, with no evidence of tumor in his bone marrow or other sites. This patient was noted to have an increase in MAGE-A3-specific T cells. This was the first report combining demethylating chemotherapy to enhance tumor antigen expression followed by a cancer antigen vaccine.

An UpToDate review on "Treatment and prognosis of neuroblastoma" (Shohet and Nuchtern, 2014) states that "Novel therapies - Development of new methods to treat high-risk neuroblastoma is an active area of research in pediatric oncology In general, novel treatments are given within a clinical trial because risks of such treatment are not fully known. Examples of therapies under investigation include immunotherapies such as anti-GD2 antibodies modified to decrease toxicities, targeted autologous T-cells, and neuroblastoma vaccines". Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Central nervous system cancers" (Version 1.2014) does not mention the use of vaccine as a management tool.

Hall et al (2013) discussed recent clinical trials using immunotherapy techniques to treat both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) and high-lighted ongoing immunotherapy research efforts at the authors' center. For NSCLC, phase II clinical trials have examined allogeneic vaccines that target either mucin 1 (MUC1), epidermal growth factor or melanoma-associated antigen 3. These vaccines are now undergoing larger phase III trials. An autologous cellular therapy directed against transforming growth factor beta-2 and a recombinant protein with antitumor properties have also shown promise in prolonging survival in NSCLC in phase II trials. The monoclonal antibodies ipilimumab, BMS-936558 (anti-PD-1), and BMS936559 (anti-PD-L1) lead to enhanced T-cell-mediated anti-tumor effects and have produced objective responses in early-phase clinical trials. Studies for SCLC also exist, such as a novel vaccine therapy targeting p53. The authors concluded that recent clinical trials in lung cancer demonstrated the potential of immunotherapeutics to increase overall survival in patients with lung cancer compared with the current standard of care.

An UpToDate review on "Immunotherapy for non-small cell lung cancer" (Gettinger, 2014) states that "Several other vaccines are currently being evaluated in Phase III studies. Additional efforts are concentrating of developing new vaccines and combining vaccines with other immunologic agents, chemotherapy or targeted agents. Advances in DNA and RNA sequencing and drug development may also ultimately allow for the creation of personalized vaccines consisting of several antigens uniquely expressed by an individual's tumor Two immunotherapeutic approaches showing promise in NSCLC are immune checkpoint inhibition and cancer vaccination. Multiple agents are currently in advanced clinical development, and the results of ongoing randomized clinical trials will define the role of immunotherapy in the treatment of NSCLC". Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Non-small cell lung cancer" (Version 3.2014) does not mention the use of vaccine as a management tool.

In a phase II clinical trial, Morse et al (2013) examined if 1 of 2 vaccines based on dendritic cells (DCs) and poxvectors encoding CEA (carcinoembryonic antigen) and MUC1 (PANVAC) would lengthen survival in patients with resected metastases of colorectal cancer (CRC). Patients, disease-free after CRC metastasectomy and peri-operative chemotherapy (n = 74), were randomized to injections of autologous DCs modified with PANVAC (DC/PANVAC) or PANVAC with per injection GM-CSF (granulocyte-macrophage colony-stimulating factor). End-points were recurrence-free survival, overall survival (OS), and rate of CEA-specific immune responses. Clinical outcome was compared with that of an unvaccinated, contemporary group of patients who had undergone CRC metastasectomy, received similar peri-operative therapy, and would have otherwise been eligible for the study. Recurrence-free survival at 2 years was similar (47 % and 55 % for DC/PANVAC and PANVAC/GM-CSF, respectively) ($\chi^2 P = 0.48$). At a median follow-up of 35.7 months, there were 2 of 37 deaths in the DC/PANVAC arm and 5 of 37 deaths in the PANVAC/GM-CSF arm. The rate and magnitude of T-cell responses against CEA was statistically similar between study arms. As a group, vaccinated patients had superior survival compared with the contemporary unvaccinated group. The authors concluded that both DC and poxvector vaccines had similar activity. Survival was longer for vaccinated patients than for a contemporary unvaccinated group, suggesting that a RCT of poxvector vaccinations compared with standard follow-up after metastasectomy is warranted.

Ding and Ming (2014) noted that lung cancer is the most common malignancy worldwide in terms of incidence and mortality. The vast majority of cases (85 to 90 %) are NSCLC. Immunotherapy consists of mainly therapeutic vaccination designed to induce or amplify the immune responses directed against tumor-associated antigens. However, there is no conclusion to date for its strengths and weaknesses. Assessing the objective safety and effectiveness of the therapeutic vaccination for NSCLC patients will help to figure out the future development of therapeutic vaccination. These investigators performed a meta-analysis of 6 RCTs including 2,239 patients (1,363 patients in the therapeutic vaccination group and 876 patients in the control group) with NSCLC. Quantitative analysis was carried out to evaluate OS and toxicity of therapeutic vaccination. The vaccine group had produced significant improvement in OS compared with the control group (hazard ratio [HR] 0.83, 95 % confidence interval [CI]: 0.76 to 0.91; $Z = 3.79$, $p = 0.0002$). Subgroup analysis showed a more significant improvement of OS in the subgroup compared with the control group (HR 0.70, 95 % CI: 0.59 to 0.82; $Z = 4.42$, $p < 0.00001$). No increased incidence of adverse events was obtained in the therapeutic vaccination group compared with the control group. The authors concluded that therapeutic vaccination added benefits to NSCLC patients and may become a standard complementary therapeutic approach in the future if the associated toxicity is reduced.

Wang et al (2014) stated that glioblastoma multiforme (GBM) has a poor prognosis. In a systematic review and meta-analysis, these investigators analyzed the outcomes of clinical trials that compared immunotherapy with conventional therapy for the treatment of malignant gliomas. PubMed, Cochrane and Google Scholar databases were searched for relevant studies. The 2-year survival rate was used to evaluate effectiveness of immunotherapy. Of 171 studies identified, 6 comparative trials were

included in the systematic review. Immunotherapy was associated with a significantly longer OS and 2-year survival compared to conventional therapy. The authors concluded that immunotherapy may improve the survival of patients with GBM.

Kobayashi et al (2014) stated that DC-based cancer vaccines may have a significant benefit to patients with advanced pancreatic cancer. However, variations among clinical studies make it difficult to compare clinical outcomes. These investigators identified factors that determined the clinical benefits by analyzing data obtained at 7 Japanese institutions that employed the same DC preparation and treatment regimens. Of 354 patients who met the inclusion criteria, 255 patients who received standard chemotherapy combined with peptide-pulsed DC vaccines were analyzed. The mean survival time from diagnosis was 16.5 months (95 % CI: 14.4 to 18.5) and that from the first vaccination was 9.9 months (95 % CI: 8.0 to 12.9). Known prognostic baseline factors related to advanced pancreatic cancer, namely ECOG-PS, peritoneal metastasis, liver metastasis, and the prognostic nutrition index, were also representative. Importantly, these researchers found that erythema reaction after vaccination was an independent and treatment-related prognostic factor for better survival and that OK-432 might be a good adjuvant enhancing the anti-tumor immunity during DC vaccination. The authors concluded that this was the first report of a multi-center clinical study suggesting the feasibility and possible clinical benefit of an add-on DC vaccine in patients with advanced pancreatic cancer who are undergoing chemotherapy. They stated that these findings need to be addressed in well-controlled, prospective randomized trials.

Helper Multi-Peptide (6MHP) Vaccine for Metastatic Melanoma

Hu and colleagues (2015) stated that a multi-peptide vaccine (6MHP), designed to induce helper T cells against melanocytic and cancer-testis antigens, has been shown to induce specific Th1-dominant CD4+ T cell responses. These researchers compared the long-term outcome of patients with metastatic melanoma vaccinated with 6MHP to that of a group of unvaccinated historical controls. The 6MHP vaccine was given to patients with metastatic melanoma. Circulating CD4+ T cell responses were measured by proliferation or direct IFN-gamma ELISpot assay. Overall survival of vaccinated patients was compared to a group of clinically comparable historical controls using multi-variable Cox regression analysis and Kaplan-Meier survival analysis, taking into account age, metastatic site, and resection status. Across 40 vaccinated patients and 87 controls, resection status (HR 0.54, $p = 0.004$) and vaccination (HR 0.24, $p < 0.001$) were associated with improved OS. Forty pairs of vaccinated patients and controls were matched by metastatic site, resection status, and age within 10 years. Median survival was significantly longer for vaccinated patients (5.4 versus 1.3 years, $p < 0.001$). Among the vaccinated patients, the development of a specific immune response after vaccination was associated with improved survival (HR 0.35, $p = 0.040$). The authors concluded that helper peptide vaccination was associated with improved OS among patients with metastatic melanoma; they stated that these data support a randomized prospective trial of the 6MHP vaccine.

Tumor-Associated Antigenic Peptide-Based Vaccines for Cancers

Peres Lde and associates (2015) discussed peptide-based vaccines in breast cancer, immune responses and clinical outcomes, which include studies on animal models and phase I, phase I/II, phase II and phase III clinical trials. These researchers stated that peptide-based vaccines are powerful neoadjuvant immunotherapies that can directly target proteins expressed in tumor cells, mainly tumor-associated antigens (TAAs). The most common breast cancer TAA epitopes are derived from MUC1, HER2/neu and CEA proteins. Peptides derived from TAAs could be successfully used to elicit CD8 and CD4 T cell-specific responses. Thus, choosing peptides that adapt to natural variations of HLA genes is critical. The most attractive advantage is that the target response is more specific and less toxic than for other therapies and vaccines. Prominent studies on NeuVax - E75 (epitope for HER2/neu and GM-CSF) in breast cancer and DPX-0907 (HLA-A2-TAAs) expressed in breast cancer, ovarian and prostate cancer have shown the efficacy of peptide-based vaccines as neoadjuvant immunotherapy against cancer. The authors concluded that future peptide vaccine strategies, although a challenge to be applied in a broad range of breast cancers, point to the development of degenerate multi-epitope immunogens against multiple targets.

Nishimura and co-workers (2015) noted that recent genome-wide cDNA microarray analysis of gene expression profiles in comprehensive tumor types coupled with isolation of cancer tissues by laser-microbeam microdissection have revealed ideal TAAs that are frequently over-expressed in various cancers including head and neck squamous cell cancer (HNSCC) and lung cancer, but not in most normal tissues except for testis, placenta, and fetal organs. Pre-clinical studies using HLA-transgenic mice and human T cells in-vitro showed that TAA-derived CTL-epitope short peptides (SPs) are highly immunogenic and induce HLA-A2 or -A24-restricted CTLs. Based on the accumulated evidence, these researchers carried out a phase II clinical trial of the TAA-SP vaccine in advanced 37 HNSCC patients. This study showed a significant induction of TAA-specific CTLs in the majority of patients without serious adverse effects. Importantly, clinical responses including a complete response were observed in this study. Another phase II clinical trial of therapeutic TAA-SP vaccine, designed to evaluate the ability of prevention of recurrence, is ongoing in HNSCC patients who have received curative operations. Further studies in human pre-clinical studies and in-vivo studies using HLA class I transgenic mice showed TAA-derived long peptides (TAA-LPs) have the capacity to induce not only promiscuous HLA class II-restricted CD4(+) T helper type 1 cells but also tumor-specific CTLs through a cross-presentation mechanism. Moreover, these investigators observed an augmentation of TAA-LP-specific T helper type 1 cell responses and tumor antigen-spreading in HNSCC patients vaccinated with TAA-SPs. The authors concluded that this accumulated evidence suggested that therapeutic TAA-SPs and LPs vaccines may provide a promising cancer immunotherapy.

Chamani and colleagues (2018) noted that the E75 peptide vaccine, derived from tumor-associated antigen HER2, is the most frequently studied anti-HER2 vaccination strategy for the treatment of breast cancer patients. It has been investigated in the several phases I/II of the clinical trials and is currently being evaluated in a randomized multi-center phase III clinical trial. These researchers conducted a systematic review and meta-analysis to clarify the outcomes of the E75 peptide vaccine including the therapeutic efficacy, the disease recurrence, the survival rate, and the side effects; 3 peer-reviewed literature databases including the PubMed, Web of Science, and Scopus were sought. Of 29 trials assessed for eligibility, 16 were considered based on inclusion criteria. Statistical analyses were performed by the Excel and STATA v.11.0. Meta-analysis of delayed-type hypersensitivity (DTH) reactions and CD8⁺-T cell levels, as immune responses, displayed the significant differences in the vaccinated groups compared to their non-vaccinated counterparts. In addition, the recurrence, and the OS and the disease-free survival (DFS) were significantly different in the vaccinated subjects versus the control. The authors concluded that the valuation of the local and systemic toxicity of the E75 peptide vaccine demonstrated the minimal side effects. It appeared that the E75 peptide vaccine is safe and effective, and can be used for further randomized clinical trials.

HLA-A24-Binding Peptide Vaccines for Gastric Cancer

Fujiwara and colleagues (2017) performed a clinical trial using HLA-A24-binding peptide vaccines containing a combination of novel cancer-testis antigens and anti-angiogenic peptides for advanced gastric cancer (GC). A total of 35 GC patients who had shown resistance to the standard therapy were enrolled in this clinical trial using vaccinations with a mixture of multiple peptides derived from DEPDC1, URLC10, FoxM1, Kif20A and VEGFR1. The safety, OS, and the immunological responses based on an ELISPOT assay were determined to assess differences in patients who were HLA-A24-positive [24(+)] and HLA-A24-negative [24(-)]. No severe adverse events (AEs) were observed except for severe skin reactions in 4 patients. The differences in OS were not significant between patients who were 24(+) and 24(-). In the 24(+) group, patients who showed T cell responses specific to antigen peptides had a tendency towards better survival than those who showed no response, especially to the DEPDC1 peptide. The patients with local skin reactions had significantly better OS than the others. The authors concluded that peptide vaccine therapy was found to be safe and is expected to induce specific T cell responses in patients with advanced GC. They stated that the survival benefit of peptide vaccine monotherapy may not have been shown and further trials are needed to confirm these results.

p16(INK4a)-Based Peptide Vaccine for Human Papillomavirus-Associated Cancers

Reuschenbach and colleagues (2016) stated that the cyclin-dependent kinase inhibitor p16(INK4a) is strongly and consistently over-expressed in all human papillomavirus (HPV)-associated cancers. These researchers hypothesized that p16(INK4a) may be a vaccine target antigen for HPV-associated cancers. To test this hypothesis, these investigators performed a phase I/IIa first-in-human trial to evaluate the safety and immunogenicity of a p16(INK4a)-based peptide vaccine. A total of 26 patients with different, advanced, p16(INK4a)-overexpressing, HPV DNA-positive cancers were included after the completion of standard treatment. According to protocol, 12 subcutaneous injections of a p16(INK4) peptide (P16_37-63) mixed in a water-in-oil emulsion with immuno-adjuvant activity (Montanide ISA-51 VG) were administered over a 6-month period. A total of 20 patients received at least 4 injections and were evaluable for immune responses against P16_37-63. Clusters of differentiation (CD) 4 T cells were detected in 14 of 20 patients (3 of whom had pre-existing CD4 T cells before vaccination), CD8 T cells were detected in 5 of 20 patients, and antibodies were detected in 14 of 20 patients (1 of whom had pre-existing antibodies). No suspected unexpected serious adverse reaction or serious adverse drug reaction was documented. All reported serious AEs were expected and not considered to be related to study therapy. None of the patients discontinued trial participation due to unacceptable toxicities and no dose-limiting toxicities occurred. Tumor response could be assessed in 14 patients. Of these, 9 patients (64 %) had stable disease (SD) as their best overall response and 5 patients (36 %) developed progressive disease. The authors concluded that vaccination with the p16(INK4a)-derived peptide P16_37-63 appeared to induce cellular and humoral immune responses and did not cause severe toxicities. They stated that the findings of the current study paved the way for the further clinical development of p16(INK4a)-based cancer immuno-therapeutics.

p62 DNA Vaccine (Elenagen) for Solid Tumors (e.g., Breast, Kidney, Lung, and Ovary Cancers as well as Melanoma)

Ponomarenko and colleagues (2017) noted that Elenagen is a plasmid encoding p62/SQSTM1, the first DNA vaccine possessing 2 mutually complementing mechanisms of action:

1. it elicits immune response against p62, and
2. it mitigates systemic chronic inflammation.

Previously, Elenagen demonstrated anti-tumor safety and effectiveness in rodent tumor models and spontaneous tumors in dogs. This multi-center phase I/IIa clinical trial evaluated safety and clinical activity of Elenagen in patients with advanced solid tumors. A total of 15 patients were treated with escalating doses of Elenagen (1 to 5 mg per doses, 5 times weekly) and additional 12 patients received 1-mg dose; 10 patients with breast and ovary cancers that progressed after Elenagen were then treated with conventional chemotherapy; AEs were of Grade 1; no severe AEs were observed. Cumulatively, 12 patients (44 %) with breast, ovary, lung, renal cancer and melanoma achieved SD for at least 8 weeks, with 4 of them (15 %) had tumor control for more than 24 weeks, with a maximum of 32 weeks. Patients with breast and ovary cancers achieved additional tumor

stabilization for 12 to 28 weeks when treated with chemotherapy following Elenagen treatment. The authors concluded that Elenagen demonstrated good safety profile and anti-tumor activity in advanced solid tumors; especially encouraging is its ability to restore tumor sensitivity to chemotherapy. These preliminary findings need to be validated by well-designed phase III studies.

Vaccine for Ovarian Cancer

In a pilot clinical trial, Tanyi and co-workers (2018) tested a personalized vaccine generated by autologous DCs pulsed with oxidized autologous whole-tumor cell lysate (OCDL), which was injected intranodally in platinum-treated, immunotherapy-naïve, recurrent ovarian cancer patients. OCDL was administered alone (cohort 1, n = 5), in combination with bevacizumab (cohort 2, n = 10), or bevacizumab plus low-dose intravenous cyclophosphamide (cohort 3, n = 10) until disease progression or vaccine exhaustion. A total of 392 vaccine doses were administered without serious AEs. Vaccination induced T cell responses to autologous tumor antigen, which were associated with significantly prolonged survival. Vaccination also amplified T cell responses against mutated neoepitopes derived from non-synonymous somatic tumor mutations, and this included priming of T cells against previously unrecognized neoepitopes, as well as novel T cell clones of markedly higher avidity against previously recognized neoepitopes. The authors concluded that the use of oxidized whole-tumor lysate DC vaccine is safe and effective in eliciting a broad anti-tumor immunity, including private neoantigens, and warrants further clinical testing.

Vaccine for Pancreatic Cancer

Yanagisawa and associates (2018) noted that Wilms' tumor 1 (WT1) is a tumor-associated antigen highly expressed in cancer. These researchers examined the safety of WT1-peptide pulsed DC (WT1-DC) vaccine in combination with chemotherapy in patients with surgically resected pancreatic cancer. A total of 8 patients with resectable pancreatic cancer undergoing surgery either combined with S-1 or S-1 plus gemcitabine therapy were enrolled. Immunohistochemical analysis of WT1 was performed in 34 cases of pancreatic cancer. No serious side-effects were observed, except grade I fever in 5 and grade I reactions at the injection site in all patients. WT1-specific cytotoxic T-lymphocytes were detected in 7 patients, and WT1 and HLA class I antigens were positive in all 34 cases. The authors concluded that the findings of this study clarified the safety and potential acquisition of immunity after vaccination targeting WT1. Moreover, they stated that further efficacy of WT1-DC vaccine to improve prognosis would be determined by a prospective clinical trial for resectable pancreatic cancer.

Gugulothu et al (2024) stated that advanced pancreatic cancer is one of the prominent contributors to cancer-related mortality worldwide. Chemotherapy, especially gemcitabine, is generally used for the treatment of advanced pancreatic cancer. Despite the treatment, the fatality rate for advanced pancreatic cancer is alarmingly high; therefore, there is a need for better therapeutic alternatives that has drawn focus to cancer vaccinations. The Wilms tumor gene (WT1), typically associated with Wilms tumor, is found to be excessively expressed in some cancers, such as pancreatic cancer. This characteristic feature is harvested to develop cancer vaccines against WT1. These researchers examined the clinical trials investigating the safety and effectiveness of WT1 vaccines in patients with advanced pancreatic cancer. They carried out a literature search on databases Medline, Web of Science, ScienceDirect, and Google Scholar using the keywords "advanced pancreatic cancer", "cancer vaccines", "WT1 vaccines," and "pulsed DC vaccines", and the results were studied to construct this review. WT1 vaccines work by introducing peptides from the WT1 protein to trigger an immune response involving cytotoxic T lymphocytes via antigen-presenting cells. Upon activation, these lymphocytes induce apoptosis in cancer cells by targeting those with increased WT1 levels. WT1 vaccinations, which are usually administered in addition to chemotherapy, have showed clinically positive results and minimal side effects. However, there are several challenges to their wide-spread use, such as the immunosuppressive nature of tumors and heterogeneity in expression. The authors concluded that despite being confronted with significant challenges, ongoing research into WT1 vaccines offers a promising future for cancer treatment, especially when it comes to treating advanced pancreatic cancer. Targeting the over-expressed WT1 strategically highlighted a prospective option for tailored therapies. Preliminary data suggested that WT1 vaccinations improve OS in patients with advanced pancreatic cancer, albeit the field is still in its infancy. Positive outcomes may emerge as research continues and more data becomes accessible, which could open the door for the use of WT1 vaccinations in standard care.

Vaccine for Gallbladder Cancer

Rojas-Sepulveda and colleagues (2018) stated that immunotherapy based on check-point blockers has proven survival benefits in patients with melanoma and other malignancies. However, a significant proportion of treated patients remains refractory, suggesting that in combination with active immunizations, such as cancer vaccines, they could be helpful to improve response rates. During the past 10 years, these researchers have used DC-based vaccines where DCs loaded with an allogeneic heat-conditioned melanoma cell lysate were tested in a series of clinical trials. In these studies, 60 % of stage IV melanoma DC-treated patients showed immunological responses correlating with improved survival. Further studies showed that an essential part of the clinical efficacy was associated with the use of conditioned lysates. Gallbladder cancer (GBC) is a high-incidence malignancy in South America. In this study, these investigators evaluated the feasibility of producing effective DCs using heat-conditioned cell lysates derived from GBC cell lines (GBCCL). By characterizing 9 different GBCCLs and several fresh tumor tissues, these researchers found that they expressed some tumor-associated antigens such as CEA, MUC-1, CA19-9, Erb2, Survivin, and several CEAs. Moreover, heat-shock treatment of GBCCLs induced calreticulin translocation and release of HMGB1 and ATP, both known to act as danger signals. Monocytes stimulated with combinations of conditioned lysates exhibited a potent increase of DC-maturation markers. Furthermore, conditioned lysate-matured DCs were capable of strongly inducing

CD4+ and CD8+ T cell activation, in both allogeneic and autologous cell co-cultures. Finally, in-vitro stimulated CD8+ T cells recognized HLA-matched GBCCs. The authors concluded that GBC cell lysate-loaded DCs may be considered for future immunotherapy approaches.

Vaccine for Gastric Cancer

In a phase-I/IIb, open-label, single-arm, clinical trial, Sundar and colleagues (2018) evaluated the safety, tolerability and optimal scheduling regimen of OTSGC-A24 cancer vaccine in patients with advanced gastric cancer. Patients with advanced gastric cancer with HLA-A*24:02 haplotype were included in this study. OTSGC-A24 was administered at 1 mg in 3-weekly (3w), 2-weekly (2w), and weekly (1w) cohorts to evaluate the safety, immunological response and schedule. Based on the highest specific cytotoxic T lymphocyte (CTL) induction rate at 4 weeks, using the ELISPOT test, cohorts were expanded to define the optimal dosing schedule for OTSGC-A24. A total of 24 advanced gastric cancer patients with HLA-A*24:02 haplotype were enrolled and treated in 3 cohorts (3w cohort: n = 3; 2w cohort: n = 11 and 1w cohort: n = 10 patients). The most common AEs were decreased appetite (29 %), diarrhea (21 %), myalgia (25 %). The most common treatment-related AE was injection site erythema (25 %). No dose-limiting toxicities (DLTs) were observed in any cohort and OTSGC-A24 was well-tolerated. Positive CTL responses after vaccination were observed in 15 patients (75 %) at 4 weeks: 3w cohort (33 %), 2w cohort (88 %), 1w cohort (78 %). At 12 weeks, 18 patients had responded (90 %); 3w cohort (100 %), 2w cohort (100 %), 1w cohort (78 %). The best radiological was SD (40 %); median progression free survival (PFS) was 1.7 months (95 % CI: 1.4 to 3.5) and median OS was 5.7 months (95 % CI: 3.8 to 8.6). The authors concluded that OTSGC-A24 combined peptide cancer vaccine was well-tolerated. Significant responses in CTL were observed and the recommended phase-II dose is 1 mg OTSGC-A24 sub-cutaneous, every 2 weeks. Although no radiological response was observed, a respectable OS was achieved, consistent with other immunotherapy agents being investigated in gastric cancer.

Vaccine for Glioma

Platten and associates (2018) reviewed the current state of glioma vaccine development and highlighted the challenges associated with clinical implementation of these approaches. Vaccination strategies against gliomas have matured considerably during the past years, although proof-of efficacy from controlled clinical trials is still lacking. Advances in antigen discovery, including the definition of neoepitopes including epidermal growth factor receptor variant III (EGFRvIII), isocitrate dehydrogenase (IDH)1R132H and histone (H)3.3K27M, using multi-omic approaches and computational algorithms allow targeting single antigens, but also implementing truly personalized approaches. In addition, new concepts of vaccine manufacturing including RNA and DNA vaccines improve immunogenicity and applicability in personalized settings. The authors concluded that as an increasing amount of clinical data defy the concept of the central nervous system (CNS) as a strictly immuno-privileged site, novel vaccine approaches enter the clinic including critical efforts to identify biomarkers of response and resistance and strategies to overcome the immunosuppressive glioma microenvironment.

Vaccine for Oral Squamous Cell Carcinoma

Dong and co-workers (2018) stated that due to the high-quality immunogenicity of tumor-derived autophagosomes (DRibbles), these researchers examined the anti-tumor ability and mechanism of DRibble-loaded dendritic cells (DRibble-DCs). DRibbles extracted from the oral squamous cell carcinoma cell line SCC7 express specific LC3-II and ubiquitination marker. Immunization of mice with the DRibble-DCs vaccine led to the proliferation and differentiation of CD3+CD4+IFN- γ + and CD3+CD8+IFN- γ + T cells. The expression of proteins in endoplasmic reticulum stress (ERS) pathways was determined by Western blot. Additionally, the functional properties of the DRibble-DCs were examined in mice, and regulatory T cells were measured by flow cytometry. Excellent biocompatibility was observed in-vitro when DCs were loaded with DRibbles. T cells of lymph nodes and spleens from mice immunized with DRibble-DCs had cytotoxic effects on SCC7 cells. DCs homeostasis and ERS-related proteins were affected by DRibbles. Moreover, the DRibble-DCs vaccine achieved significantly better anti-tumor efficacy than DRibbles and tumor cell lysate-loaded DCs. The authors concluded that these findings validated the anti-tumor immune responses to the DRibble-DCs vaccine in-vivo and in-vitro; the ERS pathway can be affected by DRibbles.

Vaccine for Breast Cancer

Singer and colleagues (2020) noted that immune-based strategies represent a promising approach in breast cancer (BC) treatment. The glycoprotein mucin-1 (MUC-1) is over-expressed in more than 90 % of BC patients, and is targeted by the cancer vaccine tecemotide. In a prospective, randomized, neoadjuvant, multi-center phase-II clinical trial, these investigators examined the safety and efficacy of tecemotide when added to neoadjuvant standard-of-care (SOC) treatment in early BC patients. A total of 400 patients with HER2-early BC were recruited into this 2-arm, phase-II study. Subjects received pre-operative SOC treatment (chemotherapy or endocrine therapy) with or without tecemotide. Post-menopausal women with estrogen receptor (ER)+++ or ER++ and Ki67 less than 14 %, and G1,2 tumors ('luminal A' tumors) received 6 months of letrozole. Post-menopausal patients with triple-negative, ER-/-/+++ and Ki67 greater than or equal to 14 %, and with G3 tumors, as well as pre-menopausal subjects, received 4 cycles of epirubicin/cyclophosphamide plus 4 cycles of docetaxel. Primary end-point was residual cancer burden (RCB; 0/I versus II/III) at surgery, and secondary end-points included pathological complete response (pCR), safety, and quality of life (QOL). These researchers observed no significant difference in RCB 0/I rates between patients with (36.4 %) and without (31.9 %) tecemotide in the overall study population (p = 0.40), nor in endocrine and chemotherapy-

treated subgroups (25.0 % versus 13.3 %, $p = 0.17$; 39.6 % versus 37.8 %, $p = 0.75$, respectively). The addition of tecemotide did not affect overall pCR rates (22.5 % versus 17.4 %, $p = 0.23$), MUC-1 expression, or tumor-infiltrating lymphocytes content. Tecemotide did not increase toxicity when compared to SOC therapy alone. The authors concluded that neoadjuvant tecemotide was safe, but did not improve RCB or pCR rates in patients receiving standard neoadjuvant therapy.

Brown and associates (2020) stated that AE37 and GP2 are HER2-derived peptide vaccines. AE37 primarily elicits a CD4+ response while GP2 elicits a CD8+ response against the HER2 antigen. These peptides were tested in a large randomized trial to examine their ability to prevent recurrence in HER2-expressing BC patients. The primary analyses found no difference in 5-year overall disease-free survival (DFS) but possible benefit in subgroups. These researchers presented the final landmark analysis. In this 4-arm, prospective, randomized, single-blinded, multi-center, phase-II clinical trial, disease-free node positive and high-risk node negative BC patients enrolled after SOC therapy; 6 monthly inoculations of vaccine (VG) versus control (CG) were administered as the primary vaccine series with 4 boosters at 6-month intervals. Demographic, safety, immunologic, and DFS data were evaluated. A total of 456 patients were enrolled; 154 patients in the VG and 147 in CG for AE37, 89 patients in the VG and 91 in CG for GP2. The AE37 arm had no difference in DFS as compared to CG, but pre-specified exploratory subgroup analyses showed a trend towards benefit in advanced stage ($p = 0.132$, HR 0.573, CI: 0.275 to 1.193), HER2 under-expression ($p = 0.181$, HR 0.756, CI: 0.499 to 1.145), and triple-negative BC ($p = 0.266$, HR 0.443, CI: 0.114 to 1.717). In patients with both HER2 under-expression and advanced stage, there was significant benefit in the VG ($p = 0.039$, HR 0.375, CI: 0.142 to 0.988) as compared to CG. The GP2 arm had no significant difference in DFS as compared to CG, but on subgroup analysis, HER2-positive patients had no recurrences with a trend toward improved DFS ($p = 0.052$) in VG as compared to CG. The authors concluded that the findings of this phase-II clinical trial showed that AE37 and GP2 were safe and possibly associated with improved clinical outcomes of DFS in certain subgroups of BC patients. These researchers stated that with these findings, further evaluations are needed of AE37 and GP2 vaccines given in combination and/or separately for specific subsets of BC patients based on their disease biology.

Pallerla et al (2021) noted that BC is one of the leading causes of death in women. With improvements in early-stage diagnosis and targeted therapies, there has been an improvement in the OS rate in BC over the last 10 years. Despite the development of targeted therapies, tyrosine kinase inhibitors, as well as monoclonal antibodies and their toxin conjugates, all metastatic tumors develop resistance, and nearly 1/3 of HER2+ BC patients develop resistance to all these therapies. Although antibody therapy has shown promising results in BC patients, passive immunotherapy approaches have limitations and need continuous administration over a long period. Vaccine therapy introduces antigens that act on cancer cells causing prolonged activation of the immune system. In particular, cancer relapse could be avoided due to the presence of a longer period of immunological memory with an effective vaccine that can protect against various tumor antigens. Cancer vaccines are broadly classified as preventive and therapeutic. Preventive vaccines are used to ward off any future infections and therapeutic vaccines are used to treat a person with active disease. These investigators provided details regarding the tumor environment, different types of vaccines, their advantages and disadvantages, and the current status of various vaccine candidates with a focus on vaccines for BC. Current data indicate that therapeutic vaccines themselves have limitations in terms of efficacy and are used in combination with other chemotherapeutic or targeting agents. The majority of BC vaccines are undergoing clinical trials and the next decade will see the fruitfulness of BC vaccine therapy.

Zachariah et al (2021) stated that BC prevention remains the ultimate cost-effective method to reduce the global burden of invasive BC (IBC). To-date, surgery and chemoprevention remain the main risk-reducing modalities for those with hereditary cancer syndromes, as well as high-risk non-hereditary breast lesions such as ADH, ALH, or LCIS. Ductal carcinoma in situ (DCIS) is a pre-invasive malignant lesion of the breast that closely mirrors IBC and, if left untreated, develops into IBC in up to 50 % of lesions. Certain high-risk patients with DCIS may have a 25 % risk of developing recurrent DCIS or IBC, even after surgical resection. The development of BC elicits a strong immune response, which brings to prominence the numerous advantages associated with immune-based cancer prevention over drug-based chemoprevention, supported by the success of dendritic cell vaccines targeting HER2-expressing BC. Vaccination against BC to prevent or interrupt the process of BC development remains elusive; but is a viable option. Vaccination to intercept pre-invasive or pre-malignant breast conditions may be possible by interrupting the expression pattern of various onco-drivers. Growth factors may also function as potential immune targets to prevent BC progression. In addition, neoantigens also serve as effective targets for interception by virtue of strong immunogenicity. It is noteworthy that the immune response also needs to be strong enough to result in target lesion elimination to avoid immunoediting as it may occur in IBC arising from DCIS. The authors concluded that if the issue of vaccine targets can be solved by interrupting pre-malignant lesions, there is a potential to prevent the development of IBC.

Disis and Cecil (2022) stated that BC is immunogenic; and a variety of vaccines have been designed to boost immunity directed against the disease. The components of a BC vaccine, the antigen, the delivery system, and the adjuvant, can have a significant impact on vaccine immunogenicity. There have been numerous immunogenic proteins identified in all subtypes of BC. The majority of these antigens are weakly immunogenic non-mutated tumor-associated proteins. Mutated proteins and neoantigen epitopes are found only in a small minority of patients and are enriched in the triple-negative subtype. Several vaccines have advanced to large, randomized phase-II or phase-III clinical trials. None of these trials met their primary endpoint of either PFS or OS. Despite these set-backs researchers have learned important lessons regarding the clinical application of BC vaccines from the type of immune response needed for tumor eradication, Type I T-cell immunity, to the patient populations most likely to benefit from vaccination. Many therapeutic BC vaccines are now being tested in combination with other forms of immune therapy or chemotherapy and radiation. Breast cancer vaccines as single agents are now studied in the context of the prevention of relapse or development of disease. Newer approaches are designing vaccines to prevent BC by intercepting high-

risk lesions such as DCIS to limit the progression of these tumors to invasive cancer. There are also several efforts to develop vaccines for the primary prevention of BC by targeting antigens expressed during BC initiation.

Corti et al (2022) noted that the ability to exploit the immune system as a weapon against cancer has revolutionized the treatment of cancer patients, especially through immune checkpoint inhibitors (ICIs); however, ICIs demonstrated a modest benefit in treating BC, with the exception of certain subsets of triple-negative BCs. An immune-suppressive tumor micro-environment (TME), typically present in BC, is an important factor in the poor response to immunotherapy. After almost 20 years of poor clinical trial results, cancer vaccines (CVs), an active immunotherapy, have come back in the spotlight because of some technological advancements, ultimately boosted by coronavirus disease 2019 pandemic. In particular, neoantigens are emerging as the preferred targets for CVs, with gene-based and viral vector-based platforms in development. Moreover, lipid nanoparticles proved to be immunogenic and efficient delivery vehicles. Past clinical trials examining CVs focused especially on the metastatic disease, where the TME is more likely compromised by inhibitory mechanisms. In this sense, favoring the use of CVs as monotherapy in pre-malignant or in the adjuvant setting and establishing combination treatments (i.e., CV plus ICI) in late-stage disease are promising strategies.

Vaccine for Hepatic Cancer

Zhang and colleagues (2020) stated that MAGE family genes have been studied as targets for tumor immunotherapy for a long time. These researchers combined MAGE1-, MAGE3- and MAGE4-derived peptides as a cancer vaccine and examined if a new combination nano-emulsion-encapsulated vaccine could be used to inhibit the growth of tumor cells in humanized SCID mice. The nano-emulsion-encapsulated complex protein vaccine (MAGE1, MAGE3, and MAGE4/HSP70 fusion protein; M1M3MnH) was prepared using a magnetic ultrasonic technique. After screening, human PBMCs were injected into SCID mice to mimic the human immune system. Then, the humanized SCID mice were challenged with M3-HHCC cells and immunized with nano-emulsion-encapsulated MAGE1-MAGE3-MAGE4/HSP70 [NE(M1M3MnH)] or M1M3MnH. The cellular immune responses were detected by IFN- γ ELISPOT and cytotoxicity assays. Therapeutic and tumor challenge experiments were also performed. The results showed that the immune responses elicited by NE(M1M3MnH) were apparently stronger than those elicited by M1M3MnH, NE(-) or PBS, suggesting that this novel nano-emulsion carrier induced potent anti-tumor immunity against the encapsulated antigens. The results of the therapeutic and tumor challenge experiments also indicated that the new vaccine had a definite effect on SCID mice bearing human hepatic cancer. The authors concluded that the findings of this study indicated that the combination of several tumor antigen-derived peptides may be a relatively good strategy for peptide-based cancer immunotherapy. These researchers stated that these findings suggested that the complex nano-emulsion vaccine could have broader applications for both therapy and prevention mediated by anti-tumor effects in the future.

Han et al (2023) noted that tumor vaccines for hepatocellular carcinoma (HCC) is an area of intense interest; many clinical trials have been carried out globally. However, the safety and effectiveness of tumor vaccines are elusive. In a systemic review and meta-analysis, these researchers examined the safety and effectiveness of tumor vaccines. All relevant studies were identified in PubMed, Embase, Web of science and Cochrane Library databases. Objective response rate (ORR), median OS, or median PFS and 95 % CI were meta-analyzed based on the random-effects model. The individual-level data of OS, PFS were pooled by conducting survival analysis. All observed AEs were collected. A total of 31 studies containing 35 eligible cohorts with 932 HCC patients were included. The pooled ORR were 7 % (95 % CI: 3 % to 14 %), while ORR of dendritic cell (DC) vaccine (19 %, 95 % CI: 11 % to 29 %) were highly significant than ORR of peptide vaccine (1 %, 95 % CI: 0 % to 5 %). The pooled median OS and PFS were 13.67 months (95 % CI: 8.20 to 22.80) and 6.19 months (95 % CI: 2.97 to 12.91), respectively. The pooled median OS (DC vaccine: median OS = 21.77 months, 95 % CI: 18.33 to 25.86; peptide vaccine: median OS = 10.08 months, 95 % CI: 5.23 to 19.44) and PFS (DC vaccine: median PFS = 11.01 months, 95 % CI: 5.25 to 23.09; peptide vaccine: median PFS = 1.97 months, 95 % CI: 1.53 to 2.54) of DC vaccine were also longer than that of peptide vaccine. HBV-related HCC may acquire more benefits from tumor vaccines than HCV-related HCC. In almost all studies, the observed toxicities were moderate even tiny. The authors concluded that tumor vaccines for HCC, especially DC vaccine, were safe and worth exploring. These researchers stated that more prospective, high-quality studies are needed.

Dendritic Cell-Based Cancer Vaccines

Chen and colleagues (2020) stated that the success of peptide-based dendritic cell (DC) cancer vaccines mainly depends on the utilized peptides and selection of an appropriate adjuvant. These researchers evoked a broad immune response against multiple epitopes concurrently in the presence of immunoadjuvant. Three synthetic HLA-A*0201-restricted peptides were separately linked with HMGB1-derived peptide (SAFFLFCSE, denoted as HB100-108) as immunoadjuvant via double arginine (RR) linker and loaded onto human monocyte-derived DCs. Peptide uptake was detected by immunofluorescence microscopy and flow cytometry. The maturation and activation status of pulsed DCs were monitored by detection of the expression of specific markers and released cytokines. The ability of peptide-pulsed DCs to activate allogeneic T cells has been evaluated by a degranulation assay and detection of secreted cytokines. The lytic activity of effector T cells against cancer cells in-vitro was analyzed by a lactate dehydrogenase (LDH) assay. Results revealed that DCs efficiently take up peptides+HB100-108 and expressed higher levels of surface markers (HLA-ABC, HLA-DR, CD80, CD86, CD83, CD40, and CCR7) and proinflammatory cytokines (IL-6, IFN- γ , TNF- α , and IL-12) than control DCs, free peptide-pulsed DCs, and free HB100-108-pulsed DC groups. Moreover, peptides+HB100-108/pulsed DCs were capable of activating allogeneic T cells and enhance their lytic activity against a pancreatic cancer cell line (PANC-1) in-vitro. The authors concluded that these findings suggested that antigenic peptides covalently linked with HB100-108/pulsed DCs could be a promising strategy to improve the current DC-based cancer vaccines.

Whole Cancer Stem Cell-Based Vaccines for the Surgical Management of Solid Tumors

In a systematic review and meta-analysis of RCTs, Bastin et al (2023) examined the safety and effectiveness of autologous whole cell vaccines as immunotherapies for solid tumors. The primary safety outcome was number, and grade of AEs. The primary effectiveness outcome was clinical responses. Secondary outcomes included survival metrics and correlative immune assays. These investigators searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for studies published between 1946 and August 2020 using any autologous whole cell product in the treatment of any solid tumor. The Cochrane Randomized Controlled Trial risk of bias tool was used to assess risk of bias. A total of 18 studies were identified with a total of 714 patients enrolled in control and 808 in vaccine arms. In 698 patients receiving at least 1 dose of vaccine, treatment was well-tolerated with a total of 5 grade-III or higher AEs. Clinical response was reported in a minority ($n = 2$, 14 %) of studies. Autologous whole cell vaccines were associated with improved OS (HR 1.28, 95 % CI: 1.01 to 1.63) and DFS (HR 1.33, 95 % CI: 1.05 to 1.67) over 13 and 10 trials, respectively. Where reported, immune assays correlated well with clinical outcomes. The authors concluded that the findings of this systematic review/meta-analysis suggested that autologous whole cell vaccination was safe and effective in increasing survival in patients undergoing treatment for solid tumors. Moreover, these researchers stated that this review was limited by the broad publication range, limited power to make conclusions in any one disease site, and inconsistencies in reporting standards across studies. Given the significant advances that have been made in basic tumor immunobiology and immunotherapy as a field in the past 10 years, there is strong rationale to continue examining autologous whole cell vaccines as an adjuvant strategy to the surgical management of solid tumors.

The authors stated that a major drawback of this study was the variability in terms of protocols and time periods during which trials were carried out; half of the 18 reports captured in this systematic review were published before 2000 with the remaining being published subsequently. Technical knowledge, reporting standards, and the ability to accurately evaluate residual disease have advanced considerably. Knowledge of tumor immunology and cancer immunotherapy has also expanded significantly over the timeframe in which studies were published; thus, it is less informative to rely on quantitative outcomes reported in earlier studies than it is to consider the overall trends that were established. The variability in disease sites investigated, while reducing the power of the report to make conclusions regarding any one tumor type, provides a broader overview of the effectiveness of autologous whole cell vaccination. While comparison between outcomes in different disease sites can be performed based on the analysis, it is most reliable in studies that carried out comparisons in the setting of a single trial.

Hashemi et al (2023) stated that despite the conventional cancer therapeutic, cancer treatment remains a medical challenge due to neoplasm metastasis and cancer recurrence; thus, new approaches promoting therapeutic strategies are highly desirable. As a new therapy, the use of whole neoplastic stem cells or cancer stem cell (CSC)-based vaccines is one strategy to overcome these obstacles. These investigators examined the effects of whole CSC-based vaccines on the solid tumor development, metastasis, and survival rate. Primary electronic databases (PubMed/Medline, Scopus, Embase, and Web of Science) and a major clinical registry were searched. Interventional studies of whole CSC-based vaccines in rodent cancer models (38 studies) and human cancer patients (11 studies) were included; the vaccine preparation methodologies, effects, and overall outcomes were evaluated. Pre-clinical studies were divided into 4 groups: CSC-lysates/inactivated-CSC-based vaccines, CSC-lysate-loaded dendritic cell (CSC-DC) vaccines, cytotoxic T-cell (CTL) vaccines generated with CSC-DC (CSC-DC-CTL), and combinatorial treatments performed in the prophylactic and therapeutic experimental models. The majority of pre-clinical studies reported a promising effect on tumor growth, survival rate, and metastasis. Moreover, whole CSC-based vaccines induced several anti-tumor immune responses. A small number of clinical investigations suggested that the whole CSC-based vaccine treatment was beneficial; however, further research is needed. The authors concluded that this comprehensive review provided an overview of the available methods for examining the effectiveness of whole CSC-based vaccines on tumor development, metastasis, and survival rate. Furthermore, it presented a set of recommendations for designing high-quality clinical trials that may allow to determine the effectiveness of whole CSC-based-vaccines in cancer therapy.

Vaccine for Acute Myeloid Leukemia

Khanmiri et al (2024) noted that acute myeloid leukemia (AML) is classified as a hematologic malignancy characterized by the proliferation of immature blood cells within the bone marrow (BM), resulting in an aberrant and unregulated cellular growth. The primary therapeutic modalities for AML include chemotherapy and hematopoietic stem cell transplantation (HSCT); however, it is important to note that these treatments are accompanied by important adverse effects and mortality rates. Thus, the need for more effective therapeutic options is necessary, and DC vaccine therapy can be one of these options. These investigators examined the effectiveness of DC vaccination therapy for the management of AML. PubMed, Scopus, ProQuest, Web of Science, and Google Scholar databases were searched for this systematic review. The articles were evaluated based on the inclusion criteria of this study and initially compared in terms of titles or abstracts. Finally, the articles related to the topic of this review were obtained in full text. The complete remission (CR) and partial remission (PR), survival, correlative immune assays, and health-related metrics were used to evaluate this cellular immunotherapy effectiveness. The quality of the studies was assessed independently using the Cochrane risk-of-bias tools. The compiled data were input into a standard Excel spreadsheet. Each domain was evaluated as having either a "low risk", "high risk", or "unclear risk" of bias. Among the 3,986 studies that were determined, a total of 11 correlated trials were selected for inclusion in this systematic review. DC vaccine therapy was effective in inducing CR and PR, and stabilization of the disease. Furthermore, it was discovered that the treatment strengthened the immune system as indexed by increased levels of CD4+ and CD8+ T cells, Th1 cytokines, WT1-specific T cells, and activated NK cells. The authors concluded that the findings of this systematic review support the use of DC vaccine therapy as an effective treatment for AML; it showed potentials in achieving remission, enhancing the immune system function,

and increasing OS. Moreover, these researchers stated that more studies are needed to improve the methods of preparing and delivering the DC vaccine, and to confirm its long-term safety and effectiveness.

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The above policy is based on the following references:

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Policy History

- Last Review 08/15/2024

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Next Review: 06/12/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes