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Vaccines Against Different Types of Cancer: Literature Review

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ABSTRACT

According to the World Health Organization, in 2018, cancer was considered the second leading cause of death in the world, corresponding to 9.6 million deaths. Faced with this situation, some alternatives to combat tumors in some organs were developed, such as immunotherapy involving vaccines. Among the vaccines already developed, Sipuleucel-T (Provenge®) can be mentioned, that has been approved by the Food and Drug Administration in 2010 for cases of metastatic prostate cancer; prophylactic bivalent and quadrivalent vaccines to human papillomavirus; the nanoparticulate liposomal RNA vaccine, the melanoma FixVac (BNT111); peptide-based vaccines, such as carcinoembryonic antigen, and those that involve antigen-loaded dendritic cells for the treatment of colorectal cancer, as well as colorectal cancer stem cell-based vaccines and, for cases of ovarian cancer, dendritic cell vaccines. In relation to breast cancer, research is aimed at both immunotherapy with dendritic cells pulsed with tumor antigens and vaccines that have a combined therapy of dendritic cells and Natural Killer cells. In general, vaccines promote the induction of helper and cytotoxic cells to thereby eliminate tumor cells. This characteristic of using dendritic cells with tumor antigens already processed and presented on the cell surface allows the questioning about the use of the term "vaccine", since it does not correspond to conventional vaccines. Thus, the studies carried out in this area of immunotherapy, although complex and expensive, show promise in the treatment of several types of cancer, with great possibilities of positively impacting the lives of all those who suffer from the disease.

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Introduction

Cancer is a term related to malignant tumors formed by cells in disordered growth that tend to invade nearby tissues or to spread throughout the body. Each type is differentiated by the organ of the body it affects, the speed of cell multiplication and the ability to invade other organs. According to the World Health Organization (WHO), in 2018, cancer was considered the second leading cause of death in the world, accounting for 9.6 million deaths. The Pan American Health Organization (PAHO) points to breast, colorectal and prostate cancers as presenting the most prevalent and high mortality rate, and cervical cancer as the second most common type of cancer in women. Melanoma and ovarian skin cancer can be more lethal if not diagnosed early [1,2].

The activation of CD8+ cytotoxic T lymphocytes (CTL) represents the main defense mechanism of the immune system against cancer cells involving adaptive immunity. CTLs recognize the antigens presented through MHC class I. It is believed that CD4+ T cells may also be involved through the secretion of cytokines, such as TNF and IFN-gamma, inducing increase of the expression of MHC class I by tumor cells and contributing to the activation of M1 macrophages. Natural Killer (NK) cells, despite of not having their involvement very well elucidated, they eliminate tumor cells which present reduced MHC class I expression. Some tumor cells may also show NK activation by molecules such as MIC-A, MIC-B, and ULB, which bind to the NKG2D receptor on NK cells. In addition, the presence of IL-12 and IL-15 in the tumor microenvironment increases NK activation. The function of humoral immunity in fighting against cancer cells is not clear [3].

Although immune surveillance may be efficient, cancer cells have a great ability in evading from the immune system. Some mechanisms of tumor evasion include the loss of tumor antigen expression by selective pressure, e.g., mutations or deletions in genes that encode tumor antigens, secretion of anti-inflammatory cytokines, such as TGF-beta in high levels. Also, tumor evasion includes the activation of inhibitory pathways, such as CTLA-4 and PD-1 molecules expressed by T cells. Conventional treatment based on the use of radiotherapy and chemotherapy do not only affect cancer cells, but also healthy cells, and leads to a great number of adverse events that are very harmful to the patient [4].

Immunotherapy presents a potential strategy based on the fact that it may increase the individual's immune response (active immunotherapy) or may transfer effector cells and/or specific antibodies to the patient (passive immunotherapy). Cancer vaccines can be of different types and fit into active immunotherapy, once all of them induce memory [5].

Method

Using the Pubmed database, it was found about 300 papers regarding the use of vaccine for various types of cancers in the last 20 years. The present work proposes to review some original papers considered relevant for the reader who is interested in having a general knowledge about this very complex and important theme. A thesis and a conclusion work in Portuguese were also

included. The keywords used in the search were cancer vaccine, breast cancer vaccine, colorectal cancer vaccine, ovarian cancer vaccine, melanoma vaccine, prostate cancer vaccine, sipuleucel T, cervical cancer vaccine, human papilloma virus vaccine.

Literature Review

Breast Cancer: Currently, immunotherapy, mainly passive immunotherapy, is one of the tools against breast cancer. An example is trastuzumab, a monoclonal antibody that is used both in early stages and in metastatic cancer with overexpression of HER-2, the worst prognosis factor [6]. Regarding specific active immunotherapy, there are many studies related to therapeutic vaccines which is composed of dendritic and/or NK cells pulsed with tumor antigens. The use of dendritic cells (DC) is mainly based on their function of presenting tumor antigens to TCD8+ lymphocytes, which in turn drive tumor cells to apoptosis. Also, they present tumor antigens to CD4 positive T cells, which may contribute to the activation of CD8+T cells, macrophages, and B cells Sharma et al. [8] developed a vaccine comprised DCs pulsed with synthetic peptides like HER-2/neu, and evaluated its viability, safety, effectiveness in ductal carcinoma in situ (DCIS) [8]. In the study, 27 patients with DCIS and HER-2 / neu expression were vaccinated before surgical treatment, so that immune response in the residual tumor could be assessed. As a result, 18.5% of patients presented no residual DCIS. Of the patients with residual DCIS, 50% eliminated the antigen expression, being reported a median percentage decline of 88% in HER-2/neu expression. The combined therapy of DCs and NK cells, is based on the property of NK cells to destroy transformed cells without prior sensitization. Its interaction with DCs leads to the induction of more efficient T cell responses. Activated NK cells release IFN-gamma, which activates macrophages and stimulates Th1-polarization, increasing the cytotoxic activity against tumors Alves et al [7] evaluated a vaccine with DC and its influence on. The results showed that DCs influenced the expression of NK cell receptors, upregulating NK activation (by NKp46 and NKG2D molecules) and downregulating NK-inhibition (by Ly49g2 and NKG2A/C/E molecules) [7]. Furthermore, vaccine-treated group presented a tumor volume decrease and great production of IL-2, IL-10, IFN-γ, TNF-α and IL-12. They also evaluated the immunological profile of female Balb/c mice bearing breast cancer induced by 4T1 cells and treated with an NK cell vaccine. As a result, they observed that the vaccinated group showed higher expression of NK activation receptors and higher production of pro-inflammatory cytokines. Nonetheless, it was also observed a high expression of NK inhibitory receptors [7].

Prostate Cancer: Because of perceived severity of castration-resistant metastatic prostate cancer (CPRC), numerous drugs and alternative therapies have been studied over the years. Among the new therapies for the treatment of CPRC, the US Food and Drug Administration (FDA) approved, in 2010, the use of sipuleucel-T (Provenge®) for asymptomatic patients or for those with mild symptoms of metastatic CPRC. Sipuleucel-T is a type of active immunotherapy that aims to induce an immune response against the cancer antigens [9]. Employing a standard peripheral blood leukapheresis procedure, dendritic cells from the patient´s own blood cells are isolated and cultured ex vivo with PA2024, a fusion protein which consists of bound prostatic acid phosphatase (PAP) to macrophage colony stimulating factor (GM-CSF) [9,1,11]. After an incubation period at 37º C, autologous dendritic cells phagocytize and process the PA2024 antigen into small peptides and present them via MHC class II to CD4+ T cell receptors or via MHC class I to CD8+ T cells, stimulating the immune response against prostate tumor cells [11]. An interesting point to be questioned is the use of the term "vaccine" for sipuleucel-T. In the case of sipuleucel-T, the antigen comes into ex vivo contact with the antigen-presenting cells (APC), and, thereafter, the cells are applied into the patient in order that they will present the tumor antigens to T cells. According to FDA approval, sipuleucel-T should be administered intravenously for approximately one hour, with 30 min of observation after the procedure. In addition, it is suggested a 2-week interval between doses [10]. Shore et al [11]. reported the existence of three randomized, double-blind, phase III clinical trials, controlled by placebo, for evaluation of the effectiveness of sipuleucel-T against metastatic CPRC. In two clinical trials, entitled D9901 and D9902A, asymptomatic patients with metastatic CPRC were divided into two groups to receive three doses of Sipuleucel-T and 3-week control infusions, classified as weeks 0, 2 and 4. A volume of blood drawn from patients by leukapheresis was performed 3 days before reinfusion of the cells. The patients were followed for 36 weeks [11]. The D9901 study which included 127 patients revealed a better evolution of the disease progression in vaccinated patients compared to the controls. The D9902A study which included 98 patients also demonstrated a better evolution of the disease progression after the use of sipuleucel-T [11]. The D9902B study included 512 men with asymptomatic or metastatic CPRC with mild symptoms, divided into two groups, one vaccinated (n = 341) and one control (n = 171). The results of the study showed a 22% reduction in the risk of death, and a 31.7% probability of survival with the use of sipuleucel-T compared to 23% in the control group [10-12]. The adverse events after the use of sipuleucel-T included chills, fever, muscle pain, asthenia, headache, vomiting [10]. The results presented by the clinical trials clearly demonstrated the benefits of sipuleucel-T on survival and disease progression in patients with metastatic CPRC.

Nonetheless, the use of active immunotherapy still raises some questions regarding the best time to initiate the treatment, and possible combinations of sipuleucel-T with other therapeutic drugs. It is also necessary to take it in account the very high cost and the laboratory and clinical complexity for the use of this type of therapy, which can limit its clinical use in health centers worldwide [11,12].

Cervical cancer due to HPV: Human papillomavirus (HPV) is responsible for causing about 99% of cervical cancer, considered the second most prevalent type of cancer among women. The main representatives are the strains HPV16 and HPV18 [13]. In regard to the production of vaccines for the prevention of cervical cancer, virus-like particles (VLP) which characterize similar structures to the virus proteins, are used to stimulate humoral immune response. The genes L1 and L2 encode HPV capsid proteins which are the source of antigens employed in the vaccines used for clinical trials. It was demonstrated that L1 and L2 proteins produced by HEK293T human epithelial cell lineage previously transfected with HPV L1 and L2 genes, could be internalized in high amounts by peripheral blood mononuclear cells from healthy women (ex vivo test). The cells of the immune system [14].

According to Sakauchi et al. the presence of serum specific IgG antibodies could be detected after subcutaneous administration of HPV16 L1 and L2 proteins in Balb/c mice. Nonetheless, a greater amount of anti-L1 antibody titers was produced in comparison to anti-L2 antibody titers [15].

Among the prophylactic vaccines available worldwide, the bivalent and quadrivalent vaccines, which are responsible for prevention of infections caused by HPV 16 and 18, for instance, can be mentioned. In a study to evaluate the efficacy of the quadrivalent vaccine, it was evidenced that after its use, a significant reduction

of the prevalence of HPV types 6,11,16,18 in a group of sexually active young adult women [16].

In respect to therapeutic vaccines, sequences of peptides derived from viral proteins E6 and E7 are usually used to increase T cell stimulation in order to eliminate cervical cancer. In this way, a group of researchers outlined the use of TriVAx-HPV vaccine in a clinical trial, which is considered a therapeutic vaccine that is able to induce high numbers and long-lasting CD8+ T cells in mice. The vaccine consists of residues 49-57 of the HPV16-E7 protein mixed with polyinosinic:polycytidylic acid (poly-I:C) adjuvant and anti-CD40 co-stimulating monoclonal antibodies administered intravenously. The TriVax was responsible for inducing large T cell responses in mice against TC-1 e C3.43 tumor cells expressing HPV16-E7 [49-57] residues [13].

Another therapeutic vaccine developed to combat cervical cancer is RNA replicon- vaccine called Vvax001, which is based on the use of a recombinant replication-defective Semliki Forest virus (SFV) that encodes HPV16 E6/E7 fusion proteins. During the Phase I clinical trial, 12 participants who had a background history of cervical intraepithelial neoplasia (CIN) presented increase of CD4+ and CD8+ T cells against the E6 and E7 proteins. Greater proliferation of CD4+ T cells were demonstrated mainly in participants who received two higher doses. It should be noted that the magnitude of INF-γ production by the Th1 cell against HPV 16 observed in the study is at the same level or even at a higher level when compared to the magnitude obtained with the DNA vaccines VGX-3100 and GX-188E. Thus, it is noticeable that there are already some advances achieved mainly with prophylactic vaccines and that there are still some studies still under development when addressing the subject of therapeutic vaccines, such as RNA vaccine [17].

Melanoma: Sahin et al. propose the use of a liposomal RNA vaccine for individuals with advanced melanoma. The RNA vaccine in question is the melanoma FixVac (BNT111). Its target is associated with non-mutated tumor antigens, which are the most prevalent in melanoma [18]. An mRNA vaccine contains the genetic code for production of certain proteins, specific to the targeted disease. After their production, they will circulate and be recognized by the immune system, be processed inside the host cell and will induce an immune response against it. This immune response is represented by memory B and T cells [19]. The FixVac melanoma vaccine consists of a nanoparticulate liposomal RNA containing the coding for 4 antigens associated with melanoma, namely: New York esophageal squamous cell carcinoma 1 (NY-ESO-1), antigen associated with A3 melanoma (MAGE-A3), tyrosinase and transmembrane phosphatase with tensin homology (TPTE). It is nanoparticulate, what gives it a high power to infiltrate cells throughout the body. The genetic material of the vaccine stimulates induction of mature dendritic cells with adequate capacity of presenting melanoma antigens through MHCI and II molecules [18].

In a clinical study of the vaccine, some points were observed. After its administration, there was an increase in the use of glucose by spleen cells, thus indicating that there was a rapid targeting and transient activation of immune cells present in the lymphoid tissue. Also, it was observed an increase in the concentration of some cytokines, such as IFN-α, IFN-γ, IL- 6, IFN-inducible protein and IL-12 p70 subunit. Few adverse events were reported, for instance, fever and chills, which could be easily controlled by the use of antipyretics. Regarding T cells, the number of TCD8+ cells increased after few weeks of the vaccine administration and were targeted to many epitopes [18].

In patients who received the vaccine on a monthly schedule, T cells increased or remained stable for about one year. In individuals without continuous administration, memory T cells were present for few months. These T lymphocytes were of the effector memory phenotype PD1+; therefore, it would be necessary to block PD1 in order to increase the antitumor effect of the vaccine. The administration of the vaccine in association with an anti-PD1 therapy would be even more effective than just the vaccine [18]. Gordy et al. [20], on the other hand, proposed a vaccine using dendritic cells associated with IFN-α and a DNA methylation inhibitor. A melanoma antigen (gp 100) was conjugated to a macrophage chemokine, the 3-alpha-inflammatory protein - MIP3α. According to their results, the conjugate MIP3α-gp 100 promoted an increase in the immune response and vaccine's effectiveness. A significant reduction of the tumor was observed. Along with this, it was observed that CpG, IFNα and 5Aza were important supporting factors. A high amount of infiltrating TCD8+ lymphocytes was found 17 days after the vaccine administration [20].

Colorectal cancer: Traditional methods involving surgical procedures, chemotherapy and radiotherapy are significant, but they are not totally efficient for the treatment of colorectal cancer (CRC). According to Guo et al. According to Guo et al., it is believed that colorectal cancer stem cells (CCSCs) correspond to one of the main factors related to cancer resistance to treatment and its metastasis. Like normal stem cells, CCSCs have a high capacity for differentiation and renewal, contributing to the maintenance of cancer, in addition to their latency capacity, which can hide and provide resistance to treatment. Therefore, these cells constitute an important target for immunotherapy [21].

CCSC vaccines target a cytotoxic effector T cell response. However, it is necessary to consider the ability of these cells to deceive the immune system in order to avoid apoptosis. Also, Guo et al. Also, Guo et al. reported that during CCSC cell inactivation, a paradoxical effect can occur, that is, by eliminating their carcinogenic capacity, their ability in activating the immune system can also be affected. Therefore, strategies using cells and molecules that activate the immune system are being used, for instance, dendritic cells that present CCSCs to T cells. Anyhow, it is still necessary a better knowledge in regard to the CCSC signaling pathway and its escape mechanisms before the development of CCSC vaccines [21]. It is important to take into account that other tumor antigens such as DNA molecules, peptides and proteins may be used as targets for the vaccines.

According to Cross et al. the Myb oncoprotein is a transcription factor that has its expression increased in patients with colorectal cancer (CRC) [22]. If the factor be associated with a compatible carrier, it could be used to activate the immune system, generating a cellular immune response. Another type of vaccine is based on the use of the own patient's tumor cells. In this type of vaccine, there is an immediate recognition of the tumor antigens from the vaccine provided by immunological memory [23].

Certain peptides and proteins have increased expression in cancer cells, as is the case of the Carcinoembryonic Antigen (CEA), which is highly expressed in the CCR. In a Phase I/II clinical trial, CEA-loaded dendritic cells induced cellular immune response by cytotoxic T cells and NK cells. Mature dendritic cells arisen from monocytes of a patient with refractory cancer were incubated with a combination of OK432 (preparation containing strains of

Streptococcus pyogenes pretreated with benzathine penicillin), low-dose prostanoid and interferon alpha. The cells demonstrated a considerable capacity to activate the cells of the immune system. Although the use of tumor-associated antigens is one of the main targets of cancer vaccines, their disadvantage relies on the fact that many of the peptide antigens are also expressed in normal cells, so that the immune system shows a certain tolerance, generating a response weaker than expected [24].

In a retrospective non-randomized clinical study Zhu et al. it was demonstrated that the association of dendritic cells-containing vaccines with cytokine-induced NK cells generated a more efficient response in the treatment of renal cell carcinoma, since both innate and specific immunity were activated [25].

Nonetheless, some problems remain such as the difficulty of inducing a strong specific immune response and mechanisms of tumor evasion what guarantee a high carcinogenic and metastatic power for CCR. Nonetheless, it is also necessary to take into account the large advance of immunogenic therapy, since the development of therapeutic vaccines brings the possibility of a better prognosis for patients with CCR, including those with metastatic cancer.

Ovarian cancer: Block et al. formulated a specific dendritic cell vaccine against ovarian cancer which mechanism is to induce the Th17 profile and IL-17 secretion [26]. The target antigen includes the folate receptor alpha (FRα), which are overexpressed in high-grade serous ovarian cancer patients, a type II of tumor, and are associated with an overall survival (percentage of patients who remain alive for a certain period of time after diagnosis or initiation of treatment). The evaluation of the immune response and relapse-free survival (RFS) were performed in 18 patients in stage IIIC-IV who completed standard surgery and first-line chemotherapy. The occurrence of specific IFN- γ - producing T cells for FRα peptides and proteins increased in 89% of the patients. Similarly, the frequency of IL-17- producing T cells responsive to FRα protein increased in 78% of the patients. However, tumor antigens do not always show a good response due to their specificity and to pre-existing tolerance mechanisms [26]. For Chiang et al. own´s whole tumor lysate shows to be an alternative to initiate the cellular immune response, as it eliminates the need to search for the antigen most suitable for a particular type of cancer and the individuals can be vaccinated regardless of their HLA [27]. They first compared three preparations of different types of whole tumor lysate using mice and chose HOCl-oxidation as the obtaining method. After, a clinical study was performed to test the biological activity of pulsed dendritic cell vaccine with whole autologous tumor lysate oxidized by HOCl (OCDC vaccine) in 5 patients with recurrent ovarian cancer. The in vivo study showed that dendritic cells pulsed with HOCl-L were capable of presenting tumor-associated immunodominant epitopes, and induced the highest frequency of tumor-specific CD8+ and CD4+ T cells, achieving a better immune response [27]. This result is due to HOCl adjuvant properties on CD4+ T cells and B cells and induction of stronger MHC-II signaling, which is related to increase of immunogenicity [28].

The participants of the study had stage II/IV cancer and received 5 intranodal doses of the vaccine, except for one patient (P1) who withdrew on the 3rd dose due to disease progression [27]. For the other patients, most doses were well tolerated. Few adverse events such as flu-like symptoms were reported, attributed to systemic activation of vaccine-induced cytokines. The OCDC vaccine was able to induce high levels of cytokines and chemokines from M1 and Th1 profiles, such as IL-1Ra, IL-12, MIP-1α, MIP-1β, MCP-1, MIG, IP-10 and RANTES, and elicited both tumor-specific CD8+ T cells and CD4+ T cells. Two patients (P2 and P3) who were in clinical remission, remained in this stage for a longer period than expected, compared to historical observations of recurrent ovarian cancer treated with 2nd or 3rd line chemotherapy drugs. One of them remained in remission during 44 months. Patient 4, although presented disease progression, according to the Response Evaluation Criteria in Solid Tumors (RECIST), she had stabilization or initial regression in 6 of 13 tumor deposits and central necrosis in three additional tumor nodules which were measured as increased. There was no significant increase in tumor-reactive T cells in patient P5 after vaccination and the disease progressed [27]. On the other hand, ex vivo antigen-pulsed dendritic cells for vaccine production are more expensive and more complex. Also, they require several days to be maintained in cell culture; therefore, this type of vaccine should be restricted to specialized centers. Adams et al. investigated the potential of a vaccine based on the use of monocytes activated by Toll-like receptors (TLRM) obtained from ascites in ovarian cancer patients. Ascites monocytes were previously loaded with tumor antigen and treated with TLR4 agonist LPS [29].

The researchers [29] divided into groups with 10 animals in each as follows: a control group that received injection intraperitoneally (i.p.) or subcutaneously of CD45+ T adherent cells; a tumor-free group that received TLRM i.p. or subcutaneously; a third group which previously received tumor cells inoculation and after 3-7 days the vaccine was administered. The first two groups received the first dose of 1×10^6 cells (treated- ascites APCs or untreated cells for control group) followed by two doses of 5×10^5 cells administered in the subsequent two weeks. After 2 weeks, they received an i.p. injection of 5×10^6 ID8 tumor cells (epithelial cells from C57BL/6 mouse ovarian tissue) and remained under observation until they reached a weight of 30g due to the accumulation of ascites and were then euthanized and submitted to necropsy. The 3rd group received 4×10^6 APCs of treated ascites on day 4 after receiving tumor cell injection, followed by two 5×10^5 cell boosters of treated ascites APCs. Mice that received the i.p. vaccine with TLRM had an average survival of 81 days, whereas the mice in the untreated control group had an average survival of 40 days. The 3rd group had an average survival of 21 days. Animals that received subcutaneous injection did not show significant benefits. It was concluded that APCs activated by Toll-like receptors promote the activation of T cells and the elimination of the tumor by immune mechanisms. However, the vaccine would be more effective as a consolidation therapy after surgical debulking and primary adjuvant therapy in the scenario of minimal residual disease, thus configuring the need for more advanced studies for improvement [29].

Conclusion

Vaccines have shown to be a promising alternative as a strategy of immunotherapy against cancers. Therefore, new studies are extremely important to elucidate their immune mechanisms, their safety and effectiveness as an anti-cancer treatment. Although they are good therapeutic options, vaccines against various types of cancer are still very expensive and complex treatments, which requires both laboratory and clinical, highly qualified, which would often be a barrier for its acquisition by least developed countries. In addition, regulatory agencies, such as FDA, require well-executed clinical trials that demonstrate the real efficacy and safety of this type of treatment for their approval.

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