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Original Article

A Descriptive Clinical Oncological Analytical Research Study on the Molecular Pharmacology of Belagenpumatucel-L and Pharmaco-Oncoimmunotherapeutic Vaccines through Evidence-Based Medicine

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Abstract

Introduction: Belagenpumatucel-L, an allogeneic tumor cell vaccine, associated with the oncoimmunotherapeutic target, and transforming growth factor-β2 (TGF-β), is under clinical trial. Oncotherapeutic vaccines are used either as a substitute therapy in the treatment of chemoresistant or chemorefractory, and radioresistant or radiorefractory malignancies; or are used as a combination oncotherapy, along with chemotherapy, radiotherapy, pharmaco-immunotherapeutic targeted therapy, and surgical therapy. These modalities of onco-immunotherapy always increase the efficacy of comprehensive oncotherapy, while reducing the occurrence of frequent adverse effects caused by these oncotherapeutic regimens, otherwise. The monotherapeutic potential of pharmaco-immunotherapeutic anti-cancer vaccines is still in the investigative stages.

Objectives: This study was a descriptive clinical oncological analytical qualitative research study on belagenpumatucel-L and Pharmaco-Oncoimmunotherapeutic Vaccines.

Results: In this study, the efficacious molecular pharmacological mechanisms and potential pharmacotherapeutic significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines were analytically explored, and comprehensively elaborated, along with an emphasis on TGF-β and telomerase, as pharmacotherapeutic targets for oncotherapeutic vaccines, through an evidence-based medicine research approach.

Conclusions: In this study, the significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines, along with TGF-β and telomerase, as pharmacotherapeutic targets for oncotherapeutic vaccines were comprehensively elaborated.

Key words: Belagenpumatucel-L, Clinical oncology, Clinical research, Descriptive analytical research, Evidence-based medicine, Molecular pharmacology, Pharmaco-onco-immuno-therapeutic vaccines, Telomerase associated vaccines, TGF-β associated vaccines

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INTRODUCTION

Transforming growth factor-β2 (TGF-β) is an unique molecular pharmacological target of oncoimmunotherapeutic vaccines. The uniqueness of TGF-β is associated with the display of its paradoxical activity, as it inhibits cellular transformation and prevents cancer progression in the

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early stages of tumorigenesis, but in the later stages, it promotes tumor progression through facilitating epithelial to mesenchymal transition, stimulating angiogenesis, and inducing immunosuppression. Due to this sort of a correlated balanced synchronization of step-wise chronologically contrasting tumor promoting and tumor suppressive ability, TGF-β and its pharmacodynamic pathway have represented potential opportunities for drug development; and several therapies, including oncovaccines, targeting TGF-β pathway. Blockade of only TGF-β_1 and β_2 is sufficient to enhance the efficacy of oncovaccines, which is further increased by PD-1 checkpoint blockade immunotherapy. TGF-β enables tumor evasion of immune surveillance through various mechanisms most of which converge on the impairment of tumor cell killing by immune effector cells. Along with inhibiting proliferation and differentiation of normal bronchial epithelial cells, TGF-β mediates conversion of CD4 and CD25-T cells to T regulatory (Tregs). Serum TGF-β levels are elevated in patients with lung cancer compared to normal individuals. Elevated plasma levels of TGF-β confer a poorer prognosis for patients with lung cancer.[1-7]

Objective

The objective of this descriptive clinical oncological analytical research study was to analytically explore the molecular pharmacology of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines through an evidence-based medicine research approach.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval were taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and good clinical practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. Informed consent was obtained from the patient participants. This study involved no risk to any patient.

Study Design

The study design was a molecular pharmacological and clinical oncological multivariate, multicenter, retrospective, qualitative, descriptive, and analytical research study.

Study Population

The study population was global patients, suffering from various stages of malignancies or borderline malignancies. The study population database was a global heterogeneous multi-disciplinary experimentations and study literature on pharmaco-onco-immuno-therapeutic vaccines and belagenpumatucel-L.

Study Period

The study period was 1.5 years, from January 1999 to February 1999; January 2002 to June 2002; June 2015; April 2016 to June 2016; May 2017; and June 2021 to March 2022.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Evidence-based Medicine, Clinical Pathology, Pathology, Molecular Diagnostics, Clinical Oncology, Clinical Medicine, Respiratory Medicine, Clinical Research, Zoology, and Molecular Medicine, Dr. B. R. Ambedkar Medical College and Hospitals, J. J. M. Medical College and Hospitals, Karnataka, India; Presidency College, West Bengal, India; Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's World Enterprises, West Bengal, India, World; Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, India; Mamata Medical College and Hospitals, Telangana, India; Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India; Hi-Tech College of Nursing, Odisha, India; and Mahuya Diagnostic Centre and Doctors' Chamber, West Bengal, India.

Study Procedure

This study, a molecular pharmacological and clinical oncological multivariate, qualitative, descriptive, and analytical research study of the retrieved literature, derived through a thorough literature analysis from various available literature databases, was performed, to record, review, thoroughly analyze and delineate the molecular pharmacological basis of oncoimmunotherapeutic vaccines from a wide-ranged study literature containing molecular pharmacological researches, reviews, case presentations, and varied databases about the pharmaco-oncoimmunotherapeutic rationale of the clinical use of vaccines in the treatment of cancer patients, with a specific emphasis on telomerase and TGF-β, as molecular pharmacological targets of oncoimmunotherapeutic vaccines. After that, a multivariate evidence-based medical research study of comparative qualitative analysis of the global heterogeneous multidisciplinary experimentations and study literature on oncoimmunotherapeutic vaccines, as well as on telomerase and TGF-β, as molecular pharmacological targets of pharmaco-oncoimmuno-therapeutic vaccines, affecting global malignant and

borderline malignant patients, was conducted. This study was performed, by recording and the subsequent qualitative analyzes of oncoimmunotherapeutic vaccines, TGF-β, telomerase, and belagenpumatucel-L retrieved from the study literature database, along with selective elucidations and elaborations of the deduced study results, to derive an explicit and comprehensive interpretation of the intricate molecular pharmacological mechanisms of belagenpumatucel-L and oncoimmunotherapeutic vaccines, based on this evidence-based medicine research.

RESULTS AND DISCUSSION

This thorough qualitative analytical research study of the retrieved literature recorded from different types of medical experimentations and medical databases about oncoimmunotherapeutic vaccines, TGF-β and telomerase as molecular pharmacological targets of oncoimmunotherapeutic vaccines, and belagenpumatucel-L elaborated the following molecular pharmacological findings:

Since time immemorial, vaccines have been used to adapt the immune system to recognize pathogens, and prevent and treat diseases, such as cancer. Therapeutic cancer vaccines are attractive systemic immunotherapies that activate and expand antigen specific CD8 type and CD4 type T-cells to enhance anti-tumor immunity. Oncotherapeutic vaccines are used either as a substitute therapy in the treatment of chemoresistant or chemorefractory, and radioresistant or radiorefractory malignancies; or are used as a combination oncotherapy, along with chemotherapy, radiotherapy, pharmacoimmunotherapeutic targeted therapy, and surgical therapy. These modalities of oncoimmunotherapy always increase the efficacy of comprehensive oncotherapy, while reducing the occurrence of frequent adverse effects caused by these oncotherapeutic regimens, otherwise. The monotherapeutic potential of pharmaco-immunotherapeutic anti-cancer vaccines is still in the investigative stages. The basic cancer vaccines used include cell-based vaccines including whole cell vaccines, genetically modified tumor cell vaccine and dendritic cell vaccine, anti-idiotype antibody-based vaccine, protein- or peptide-based vaccines, heat shock protein-based vaccine, viral, bacterial or yeast vectors-based vaccines, mRNA or DNA nucleic acid-based vaccines, vaccines based on tumor associated antigens such as overexpressed proteins, differentiation antigens, cancer-testis antigens and oncofoetal antigens, and tumor specific antigens including oncogenic viral antigens, antigen presenting cells (APC) or molecular neoantigens-based vaccines with specific CD8 type T-cells and, CD4 type T-cells, and nanoparticles (NP) vectors-based vaccines. Tecemotide, a peptide vaccine targeting MUC-1 and melanoma-associated antigen-A3, a protein-based vaccine, is under clinical trials. Current bioengineering techniques make use of hydrogels, modified polymers, emulsions, liposomes, virosomes, nanodiscs, cell membranes, self-assembled proteins, virus-like particles, and nucleic acids to deliver and develop biomaterial-based vaccines, used also for personalized oncotherapy. The development of anticancer immunotherapy includes the appropriate monotherapy or combination therapy with cellular vaccines, tumor-associated antigens (TAAs), neoantigens, and chimeric antigen receptor T-cells (CAR-T).

In an evidence-based medical research study, the activities of telomerase and TGF-β on the oncovaccines have been thoroughly analyzed. While analyzing the vaccine-based strategies with TGF-β as oncotherapeutic vaccine targets, it was observed that two types of vaccines combined with TGF-β antisense have been developed, namely, belagenpumatucel-L, and gemogenovatucel-T. Belagenpumatucel-L, a non-viral gene-based allogeneic tumor cell vaccine targeting TGF-β_2, with acceptable safety profile and increased survival rate, is the first vaccine accessing the phase III trial, in non-small cell lung cancer patients. Combinational therapies with radiotherapy, chemotherapy, or immunotherapy are also in investigative phases. The previous clinical studies have shown that the treatment in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) and TGF-β_2 ASO promotes the immune response and further suppresses tumor growth. They constructed a TAG plasmid coexpressing GM-CSF and TGF-β_2 ASO, and the plasmid was incorporated into an autologous whole-cell vaccine. There were selective immune responses to the autologous TAG vaccine with >10-fold increase in IFN-γ expression over baseline. Gemogenovatucel-T is a combination of GM-CSF expression with a novel bifunctional short hairpin RNAi targeting furin convertase, involved in TGF-β_1 and β_2 precursor. In the Phase I trial, there were no adverse events, and the vaccine increased the immune response as reported in a previous study. A Phase II study was also conducted to evaluate its combination with nivolumab, a PD-1 inhibitor, in metastatic NSCLC. A Phase II with favorable 1-year survival in metastatic Ewing's sarcoma supports the justification of further testing and moving to the Phase III trial. In an ongoing Phase II trial, the maintenance of gemogenovatucel-T is investigated in women with high-risk stage ovarian cancer (IIIb-IV) following surgery and primary chemotherapy. There was high rate of induction in T-cell activation and improvement in median relapse-free survival. Considering the broad expression and roles of TGF-β_1 and TGF-β_2 in malignancy, further exploration of gemogenovatucel-T vaccine is required. This evidence-based medical research has also shown that telomerase activation is a major cell immortalization mechanism and is implicated as an essential step in carcinogenesis. Through telomerase activation, cancer

cells acquire the ability of unlimited proliferation. Telomerase activity is also linked to epithelial-to-mesenchymal transition and cancer stemness, providing cancer cells with metastatic potential. Telomerase is expressed in most tumor types across all stages of development and is thus an attractive target for therapeutic vaccination. The tumor types with increased telomerase expression combined with an immune permissive tumor microenvironment increase the therapeutic potential of telomerase targeting oncological vaccines.

Several new cancer vaccine platforms and antigen targets are under development. In an effort to amplify tumor-specific T-cell responses, a heterologous prime-boost antigen delivery strategy is increasingly used for virus-based vaccines. Viruses have also been engineered to express targeted antigens and immunomodulatory molecules simultaneously, to favorably modify the TME. Nanoparticle systems have shown promise as delivery vectors for cancer vaccines in preclinical research. T-win is another platform targeting both tumor cells and the TME, using peptide-based vaccines that engage and activate T-cells to target immunoregulatory molecules expressed on immunosuppressive and malignant cells. With the availability of next-generation sequencing (NGS), algorithms for neoantigen selection are emerging, and several bioinformatic platforms are available to select therapeutically relevant neoantigen targets for developing personalized therapies. Chemorefractory ovarian cancer has limited therapeutic options. Hence, new types of the treatment including neoantigen-specific immunotherapy need to be investigated. Neoantigens represent promising targets for personalized cancer immunotherapy. The clinical and immunological effects of a neoantigen peptide-loaded DC-based immunotherapy have been studied in a patient with recurrent and chemoresistant ovarian cancer. The reactivity against one human leukocyte antigens (HLA)-A2402-restricted neoantigen peptide derived from a mutated PPM1 F protein was detected in lymphocytes from peripheral blood by IFN-γ ELISPOT assay. Furthermore, the neoantigen (PPM1 F mutant)-specific TCRs were detected in the tumor-infiltrating T lymphocytes, post-vaccination. The results showed that vaccination with intranodal injection of neoantigen peptide-loaded DCs may have clinical and immunological impacts on cancer treatment. Neoantigens represent the long elusive immunogens for cancer vaccination. Clinical trials in melanoma and glioblastoma have demonstrated the feasibility, immunogenicity, and signals of efficacy of the personalized immunotherapy approach. Vaccines have been used to train the immune system to recognize pathogens, and prevent and treat diseases, such as cancer, for decades. Molecular-assisted precision oncology gained tremendous ground with high-throughput NGS and supported by robust bioinformatics. The quest for genomics based cancer medicine set the foundations for improved patient stratification, while unveiling a wide array of neoantigens for immunotherapy. Upfront pre-clinical and clinical studies have successfully used tumor-specific peptides in vaccines with minimal off-target effects. Alterations in protein glycosylation at the cell surface not only have functional impact on cancer progression and dissemination but also originate unique molecular fingerprints for targeted therapeutics. Immunotherapy using monoclonal antibodies and cancer vaccines is substitute strategies for colorectal cancer treatment, acting with the influence on its genetic and epigenetic alterations. When cancer immunotherapy is combined with chemotherapy, surgery, and radiotherapy, the colorectal cancer treatment would become excessively efficient, especially using bi-specific antibodies and dendritic cells mRNA vaccines. T-ALL-iPSC-based therapeutic cancer vaccine can elicit a specific anti-tumor effect on T-ALL. Glycolipids activating iNKT cells, such as α-galactosylceramide, can enhance the immune response against codelivered cancer antigens and have been applied in the design of self-adjuvanting anti-tumor vaccines. Alphavirus vectors have been engineered for the high-level gene expression relying originally on replication deficient recombinant particles, more recently designed for plasmid DNA-based administration. As alphavirus-based DNA vectors encode the alphavirus RNA replicon genes, enhanced transgene expression in comparison to conventional DNA plasmids is achieved. Immunization studies with alphavirus-based DNA plasmids have elicited specific antibody production and have generated tumor regression and protection against challenges with infectious agents and tumor cells in various animal models. A minimalist nanovaccine by formulating tumor antigen-encoding mRNA with a lipid-like material named C1 could efficiently deliver mRNA into dendritic cells with simultaneous Toll-like receptor 4 stimulation and induced T-cell activation. C1 mRNA nanovaccine exhibited significant antitumor efficacy on several tumor mouse models. The versatility and nanoscale size have helped NP improve the efficacy of conventional cancer immunotherapy and opened up exciting approaches to combat cancer. Sustained and controlled drug delivery, enhanced cross presentation by immune cells, coencapsulation of adjuvants, inhibition of immune checkpoints, and intrinsic adjuvant like properties have aided NPs to improve the therapeutic efficacy of cancer vaccines. Furthermore, NPs have been efficient modulators of TME. NPs facilitate better penetration of the chemotherapeutic drug by dissolution of the inhibitory meshwork formed by tumor associated cells, blood vessels, soluble mediators, and extra cellular matrix in TME. NPs have shown to achieve this by suppression, modulation, or reprogramming of the immune cells and other mediators localized in TME. Viral NPs are also used to generate cancer vaccines. Studies have been done to develop *in situ* cancer vaccines by enhancing

the immunomodulatory effects for immunogenic cell death (ICD) and tumor microenvironment-triggered *in situ* cancer vaccines inducing dual ICD for elevated antitumor and antimetastatic therapy. Nanovaccines are used as delivery platforms for antigens and adjuvants, which activate APCs and enhance anticancer immune responses. In a study, the therapeutic efficacy of a combinatorial treatment comprising the immunoadjuvant nanocomplex PSPEI-PIC, a DC vaccine, and PD-L1 blockade has also been studied. A study was conducted to analyze a combination of immunoadjuvant nanocomplexes and dendritic cell vaccines in the presence of immune checkpoint blockade for effective cancer immunotherapy. Nanovaccines outnumber the conventional vaccines by virtue of plasticity in physiochemical properties and ease of administration. The efficacy of nano-based vaccines may be attributed to the improved antigen stability, minimum immunotoxicity, sustained release, enhanced immunogenicity, and the flexibility of physical features of NP. Based on these, the nano-based vaccines have potential to evoke both cellular and humoral immune responses. Targeted and highly specific immunological pathways required for solid and long lasting immunity may be achieved with specially engineered nano-vaccines. Bacteria biohybrid oral vaccines for colorectal cancer treatment reduce tumor growth and increase immune infiltration. The development of anticancer immunotherapy is characterized by several approaches, the most recognized of which include cellular vaccines, TAAs, neoantigens, and CAR-T. Antigenic essence technology has also been studied as an effective means for the production of new antigen compositions for anticancer vaccination. This technology is developed *through* proteomics, cell culture technology, and immunological assays. The benefits of this technology over other approaches include the ability to control composition, optimize immunogenicity and similarity to target cells, and evade major histocompatibility complex restriction. Plasma-activated medium (PAM) potentiates the immunogenicity of tumor cell lysates for dendritic cell-based cancer vaccines. A unique atmospheric pressure plasma jet was used to prepare a PAM which induced ICD in tumor cells. This procedure increased the efficacy of tumor lysates in enhancing the immunogenicity of DCs according to their increased maturation, production of IL-12, and the capacity to induce cytotoxic CD8 T-cells able to kill tumor cells. An innovative strategy has been generated termed "biomaterial-mediated combined cell vaccines for immunotherapy," which combines tumor cell and DC vaccines with a cyclodextrin-polyethylene glycol hydrogel and a cytosine-phosphate-guanine nanoadjuvant. The nanoadjuvant promotes antigen presentation and amplifies immune-eliciting potency by codelivery of antigens and adjuvants. Combining cancer vaccines with multiple checkpoint blockade antibodies, novel multifunctional molecules, adoptive cell therapy, and immune system agonists have been used as anti-cancer combination therapies. While these combinations build on the foundation of successful immune checkpoint blockade antibodies, it is increasingly apparent that successful immunotherapy will also require a cancer vaccine backbone to engage the immune system, thereby ensuring that additional immune-oncology agents will engage a tumor-specific immune response. Human cDC1 exclusively expresses the C-type-lectin-like receptor, CLEC9A (DNGR-1) that plays an important role in cross-presentation, the process by which effective CD8 type T-cell responses are generated. CLEC9A antibodies deliver antigen specifically to cDC1 for the induction of humoral, CD4 type, and CD8 type T-cell responses and are therefore promising candidates to develop as vaccines for infectious diseases and cancer. The development of human CLEC9A antibodies now facilitates their application as vaccines for cancer immunotherapy. Tumor types possessing mechanisms of increased telomerase expression combined with an immune permissive tumor microenvironment are expected to increase the therapeutic potential of telomerase targeting cancer vaccines. Rational treatment combinations, such as checkpoint inhibitors, are likely necessary to bring out the true clinical potential of therapeutic cancer vaccines.

Belagenpumatucel-L, an allogeneic tumor cell vaccine, associated with the oncoimmunotherapeutic target, TGF-β, is under clinical trial. Belagenpumatucel-L is an allogeneic tumor cell vaccine, which consists of four irradiated NSCLC cell lines that have been modified with transforming growth factor-β2 (TGF-β2) antisense gene plasmid. TGF-β inhibits T-cell, B-cell, and dendritic cell activation, induces immunosuppressive Treg cells, and inhibits immune effector cell activation. In a Phase II study of patients with low-volume disease, belagenpumatucel-L was well tolerated, induced antibody-mediated response to vaccine HLA, and demonstrated a dose-dependent improvement in survival and response. A Phase III trial compared the efficacy of belagenpumatucel-L with placebo as a maintenance therapy in patients with stages IIIA (T3, N2 only), IIIB, and IV NSCLC without progression after up to six cycles of first-line platinum-based chemotherapy, which had to be completed 4–17 weeks before randomization. In a clinical trial, belagenpumatucel-L was administered as 2.5 × 107 cells/injection intradermally, every month for 18 months, followed by additional two quarterly injections. In a pre-planned subgroup analysis, among patients who received prior radiation therapy and enrolled within 12 weeks, belagenpumatucel-L resulted in significantly improved median overall survival.[1-7]

CONCLUSION

This study was a descriptive clinical oncological analytical qualitative research study, in which the efficacious

molecular pharmacological mechanisms and potential pharmacotherapeutic significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines were analytically explored, and comprehensively elaborated, along with an emphasis on TGF-β and telomerase as pharmacotherapeutic targets for oncotherapeutic vaccines, through an evidence-based medicine research approach. This research study aptly explained that the anticancer vaccines are appropriately effective systemic immunotherapies that systematically enhance the life-long anti-neoplastic prophylactic immunity and produce a very long-lived anti-malignant therapeutic triumph.

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