Research Article

A Descriptive Clinical Onco-pharmacological Analytical Research Study on Gemogenovatucel-T and Oncoimmunotherapeutic Vaccines in Molecular Pharmacology and Evidence-based Medicine

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ABSTRACT

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. Gemogenovatucel-T, is a combination of GM-CSF expression with a novel bifunctional short hairpin RNAi targeting furin convertase, involved in TGF-β1 and β2 precursor. This study was a descriptive clinical onco-pharmacological analytical qualitative research study, in which the efficacious molecular pharmacological mechanisms and potential pharmacotherapeutic significance of gemogenovatucel-T and pharmaco-oncoimmunotherapeutic vaccines, were analytically explored, and comprehensively elaborated, through an evidence-based medicine research approach.

Keywords: Gemogenovatucel-T, TGFβ associated vaccines, Telomerase associated vaccines, Pharmaco-onco-immuno-therapeutic vaccines, Molecular Pharmacology, Clinical Research, Descriptive Analytical Research, Evidence-Based Medicine, Clinical Onco-Pharmacology.

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INTRODUCTION

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.

TGFβ is an unique molecular pharmacological target of oncoimmunotherapeutic vaccines. The uniqueness of TGFβ is associated with the display of its paradoxical activity, as it inhibits cellular transformation and prevents cancer progression in the early stages of tumorigenesis, but in the later stages, it promotes tumour progression through facilitating epithelial to mesenchymal transition, stimulating angiogenesis and inducing immunosuppression. Due to this sort of a correlated balanced synchronization of stepwise chronologically contrasting tumour promoting and tumour suppressive ability, TGFβ and its pharmacodynamic pathway has represented potential opportunities for drug development; and several therapies, including oncovaccines, targeting TGFβ pathway. Blockade of only TGFβ1 and 2 is sufficient to enhance the efficacy of oncovaccines, which is further increased by PD-1 checkpoint blockade immunotherapy. TGF-β enables tumour evasion of immune surveillance through various mechanisms most of which converge on the impairment of tumour cell killing by immune effector cells.[1-9]

Objective

The objective of this descriptive clinical onco-pharmacological analytical research study was to explore and analyse the molecular pharmacological mechanisms of gemogenovatucel-T and pharmaco-oncoimmunotherapeutic vaccines, through an evidence-based medicine research approach.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was 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 onco-pharmacological multi-variate, multi-centre, retrospective, qualitative, descriptive, 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 heterogenous multi-disciplinary experimentations and study literature on pharmaco-onco-immuno-therapeutic vaccines and gemogenovatucel-T.

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, Obstetrics and Gynaecology, Medical and Reproductive Endocrinology, Clinical Oncology, Clinical 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 multi-variate, qualitative, descriptive, analytical research study of the retrieved literature, derived through a thorough literature analysis from various available literature databases, was performed, to record, review, thoroughly analyse and delineate the molecular pharmacological basis of oncoimmunotherapeutic vaccines and gemogenovatucel-T, 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 and gemogenovatucel-T, in the treatment of cancer patients. After that, a multivariate evidence-based medical research study of comparative qualitative analysis of the global heterogenous multidisciplinary experimentations and study literature on oncoimmunotherapeutic vaccines, and gemogenovatucel-T, affecting global malignant and borderline malignant patients, was conducted. This study was performed, by recording and the subsequent qualitative analyses of oncoimmunotherapeutic vaccines, and gemogenovatucel-T 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 gemogenovatucel-T 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, and gemogenovatucel-T elaborated the following molecular pharmacological findings:

Therapeutic cancer vaccines are attractive systemic immunotherapies that activate and expand antigen specific CD8 type and CD4 type T cells to enhance anti-tumour immunity.

There are evidences that TGFβ is an immunosuppressive cytokine produced by tumour cells and immune cells that can polarize certain immune system components within the tumour environment. During early tumour formation, transforming growth factor β can function as a tumour suppressor, to prevent tumorigenesis, but overproduction of TGFβ in established tumour is often associated with

tumour metastasis and poor prognosis in patients with cancer. The tumour promoting effects of TGFβ may be due to the immunosuppressive effects it has on both innate and adaptive immunity. TGFβ inhibits natural killer cell function by inhibiting cytokine production and downregulating the expression of activating receptors. TGFβ inhibits cytokine production and proper antigen presentation by dendritic cells, while promoting regulatory T (T_{reg}) cell differentiation and an overall tolerogenic state. TGFβ also promotes an M2 phenotype for macrophages and an N2 phenotype for neutrophils. TGFβ directly dampens the function of CD4 and CD8 type effector T cells and promotes the survival of Treg cells. Depending on the cytokines environment and their activities, TGFβ greatly affects the differentiation of several key CD4 type T cell subsets. In many studies, it has been hypothesized that blocking TGFβ induced signallng in the tumour microenvironment enhances anti-tumour immunity, which may be beneficial for cancer therapy.

In an evidence-based medical research study, the activities of telomerase and TGFβ on the oncovaccines has been thoroughly analysed. While analysing the vaccine-based strategies with TGFβ 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 nonviral gene based allogeneic tumor cell vaccine targeting TGF-β2, 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. Previous clinical studies have shown that the treatment in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) and TGF-β2 ASO promotes the immune response and further suppresses tumour growth. They constructed a TAG plasmid co-expressing GM-CSF and TGF-β2 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-β1 and β2 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 clinical trial, with favourable 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-β1 and TGF-β2 in malignancy, further exploration of gemogenovatucel-T vaccine is required. An 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 tumour types across all stages of development and is thus an attractive target for therapeutic vaccination. The tumour types with increased telomerase expression combined with an immune permissive tumor microenvironment increases the therapeutic potential of telomerase targeting oncological vaccines.

Several new cancer vaccine platforms and antigen targets are under development. In an effort to amplify tumour-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 favourably modify the TME. Nanoparticle systems have shown promise as delivery vectors for cancer vaccines in preclinical research. T-win is another platform targeting both tumour 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, 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 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 has been studied in a patient with recurrent and chemoresistant ovarian cancer. The reactivity against one 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 tumour-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 next-generation sequencing (NGS), 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 tumour-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 (mAb) and cancer vaccines are substitute strategies for colorectal cancer treatment, acting by influencing 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 (αGalCer), can enhance the immune response against co-delivered cancer antigens and have been applied in the design of self-adjuvanting anti-tumour vaccines. Alphavirus vectors have been engineered for 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, 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 (TLR4) stimulation, and induced T cell activation. C1 mRNA nanovaccine exhibited significant antitumour efficacy on several tumor mouse models. The versatility and nanoscale size have helped nanoparticles (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, co-encapsulation of adjuvants, inhibition of immune checkpoints and intrinsic adjuvant like properties have aided NPs to improve the therapeutic efficacy of cancer vaccines. Also, NPs have been efficient modulators of TME. NPs facilitate better penetration of the chemotherapeutic drug by dissolution of the inhibitory meshwork formed by tumour 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 localised in TME. Viral nanoparticles 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 immunogenic cell death for elevated antitumor and antimetastatic therapy. Nanovaccines are used as delivery platforms for antigens and adjuvants, which activate antigen-presenting cells (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 analyse a combination of immunoadjuvant nanocomplexes and dendritic cell vaccines in the presence of immune checkpoint blockade for effective cancer immunotherapy. Nano-vaccines outnumber the conventional vaccines by virtue of plasticity in physio-chemical properties and ease of administration. The efficacy of nano-based vaccines may be attributed to the improved antigen stability, minimum immuno-toxicity, sustained release, enhanced immunogenicity and the flexibility of physical features of nanoparticles. 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, tumour-associated antigens (TAAs), neoantigens, and chimeric antigen receptor T cells (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 *via* 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 potentiates the immunogenicity of tumor cell lysates for dendritic cell-based cancer vaccines. A unique atmospheric pressure plasma jet was used to prepare a plasma-activated medium (PAM) which induced immunogenic cell death 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 tumour cells. An innovative strategy has been generated termed "biomaterial-mediated combined cell vaccines for immunotherapy," which combines tumour cell and DC vaccines with a cyclodextrin-polyethylene glycol hydrogel and a cytosine-phosphate-guanine (CpG) nanoadjuvant. The nanoadjuvant promotes antigen presentation and amplifies immune-eliciting potency by co-delivery of antigens and adjuvants. Combining cancer vaccines with multiple checkpoint blockade antibodies, novel multifunctional molecules, adoptive cell therapy and

immune system agonists has 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 tumour-specific immune response. Human cDC1 exclusively express 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. Tumour types possessing mechanisms of increased telomerase expression combined with an immune permissive tumour 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.

Gemogenovatucel-T has demonstrated clinical benefit in homologous recombination proficient ovarian cancer. It is an anticancer immuno-therapeutic, which provides neoantigen education, GMCSF activation and TGFβ suppression reversal. It is a DNA engineered immunotherapy, a GMCSF/bi-shRNA furin DNA engineered autologous tumor cell product, which demonstrated safety and induction of circulating activated T-cells against autologous tumor in phase I trial. In a phase II crossover trial, it was administered in the dose of 1.0 x 10^7 cells/intradermal injection/month for 4 to 12 doses, in stage III/IV ovarian cancer patients achieving cCR, with normal imaging, CA-125.35 units/ml, physical examination, and no symptoms suggestive of the presence of active disease, following primary surgical debulking and carboplatin/paclitaxel adjuvant or neoadjuvant chemotherapy. Patients received gemogenovatucel-T or standard of care during the maintenance period. This immunotherapy had shown good safety and tolerability among patients suffering from frontline ovarian cancer. Significant induction of delay in relapse was observed, when this DNA engineered immunotherapy was administered, in comparison to controls. The high rate of induction of T cell activation was also observed, and this correlated with the clinical benefit, causing an improvement in the recurrence-free survival. While, majority of women with stage III/IV ovarian cancer who achieve clinical complete response with frontline standard of care have shown to relapse within 2 years. Gemogenovatucel-T has shown significant clinical benefit with improvement in relapse free (RFS) and overall survival (OS) in pre-planned subgroup analysis in stage III/IV newly diagnosed ovarian cancer patients with BRCA wild type (BRCA-wt) molecular profile. [1-9]

CONCLUSION

This study was a descriptive clinical onco-pharmacological analytical qualitative research study, in which the efficacious molecular pharmacological mechanisms and potential pharmacotherapeutic significance of gemogenovatucel-L and pharmaco-oncoimmunotherapeutic vaccines, were analytically explored, and comprehensively elaborated, 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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