Journal of Biomedical and Techno Nanomaterials, 1(1) - February 2024 1-7

Negative Impact of Gene Therapy on Melanoma Disease

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Received: Feb 19, 2024	Revised: Feb 22, 2024	Accepted: Feb 25, 2024	Online: Feb 27, 2024

ABSTRACT

The incidence of melanoma is rapidly increasing worldwide, posing a significant public health problem. Gene therapy for treating diseases has been discovered since 1989. Research developments to make gene therapy an effective treatment method are ongoing. Primary extracutaneous melanoma can be ocular, gastrointestinal, mucosal, leptomeningeal, genitourinary, and lymphatic. The relationship between ultraviolet (UV) exposure and the development of melanoma is highly acute and complex, and intermittent sun exposure significantly increases the risk of melanoma. It is the fifth most common type of cancer in men and the sixth in women. Mucosal melanoma is a rare disease that differs from melanoma arising elsewhere in the body. Although melanocytes are most abundant in the skin, they can also be found in smaller numbers in mucous membranes and the eyes. There are epidemiological, genetic, and physiological differences between melanomas arising from melanocytes in these various locations, and these differences have important implications for both disease prognosis and treatment.

Keywords: *Gene Therapy, Negative Impact, Melanoma Disease*

Journal Homepage https://journal.ypidathu.or.id/index.php/ijnis

How to cite: Inzagi, Z, A, N., Samasta, A, N., A'la, G, D & (2024). Negative Impact of Gene Therapy on Melanoma Disease. *Journal of Biomedical and Techno Nanomaterials*, 1(1), 1-7. https://doi.org/10.55849/jbtn.v1i1.172
Published by: Yayasan Pedidikan Islam Daarut Thufulah

INTRODUCTION

Melanoma is one of the most serious types of skin cancer, originating from melanocytes located in the epidermis or dermis of the skin. Additionally, melanoma can arise from melanocytes in other parts of the body such as the eyes, meninges, gastrointestinal tract, mucosa, or lymph nodes. Although there is no definitive cause for melanoma, irregular sun exposure is often associated with an increased risk of this disease. Over the past 35 years, the incidence of melanoma has increased, with the average age at diagnosis being around 53 years. Melanoma is more common in white individuals than in people of color, and the five-year survival rate for cutaneous melanoma has improved

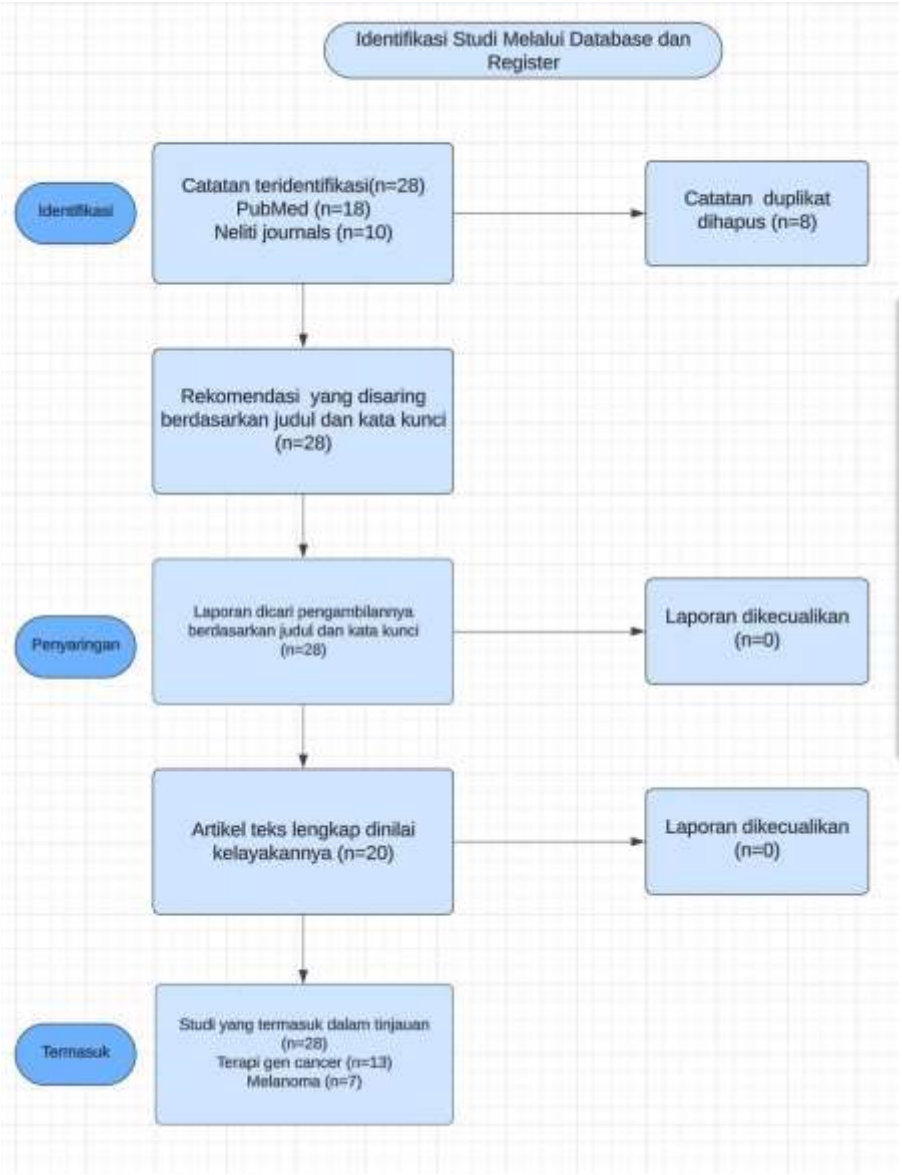
since 1976. There are four types of melanoma: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Clinical signs of melanoma include asymmetry, border irregularity, color variation, increased diameter, elevation, ulceration, and bleeding in pigmented lesions. Histopathological findings such as tumor thickness, tumor invasion, surface ulceration, spread to lymph nodes, and metastasis are used to estimate patient prognosis. The incidence of cutaneous melanoma is increasing, with a faster rise observed in men compared to other malignancies, and in women as well, except for lung cancer. According to GLOBOCAN data from 2018, the number of new global melanoma cases reached approximately 287,723 annually, with 60,712 deaths attributed to it. The highest incidence rate occurs in Queensland, Australia, with 56 cases per 100,000 men per year and 41 cases per 100,000 women per year. For white individuals in the United States, the incidence rate of melanoma is about 19 cases per 100,000 men and 14 cases per 100,000 women annually. Roughly, around 86% of melanoma cases can be attributed to ultraviolet (UV) exposure from the sun. The malignancy of pigment-producing cells (melanocytes), primarily located in the skin but also found in the ears, gastrointestinal tract, eyes, oral and genital mucosa, and the leptomeningeal layers.

Gene therapy offers new hope in the treatment of melanoma by leveraging a deep understanding of the genetic mechanisms underlying the disease to develop more effective and targeted treatment strategies. Gene therapy technology is based on the principles of genetic engineering to create genetically modified organisms (GMOs), also known as transgenic organisms. The concept of gene therapy involves the addition of normal genes to a mutated or damaged section of the genome with the goal of restoring the function of those genes. Gene therapy was first applied on September 14, 1990, in the United States to treat adenosine deaminase (ADA) deficiency in severe combined immunodeficiency (SCID). The use of ADA gene transfer in patients' cells improved their immunity. Subsequently, more than 600 gene therapy clinical trials have been conducted worldwide, with over 4,000 patients undergoing the procedure. Since then, there have been more than 600 clinical trials conducted globally, with over 4,000 patients having received gene therapy. Researchers see the potential of gene therapy as a solution to cancer, a condition caused by abnormalities in gene regulation and expression. Although chemotherapy and radiotherapy can improve survival rates and yield positive outcomes in cancer treatment in some cases, they have significant drawbacks. Chemotherapy targets only proliferating cells, not cancer cells specifically. Additionally, chemotherapy has serious side effects, limiting its dosage, and in most solid tumor cases, cancer can quickly recur after therapy. Compared to conventional methods, gene therapy for cancer offers more specific treatment, lower toxicity, and greater curative potential

In this article, the researchers focus on the negative impacts of gene therapy on melanoma. The article aims to inform readers about the adverse effects of gene therapy on melanoma. Additionally, the article seeks to educate readers about gene therapy and melanoma.

RESEARCH METHODOLOGY

The search for this article was conducted for research published before May 30, 2023, using three databases: PubMed, Journals Neliti, and Google Scholar. The keywords used were "Gene Therapy" and "Melanoma," with detailed searches including "Gene Therapy" (all fields) and "Melanoma" (all fields). Google Scholar was utilized to complement the literature search. This approach was used to broaden the search scope with relevant references from Google Scholar, using predefined inclusion and exclusion criteria to ensure relevant and high-quality search results.



RESULT

Melanoma often has properties that stimulate the immune system. Lesions that have spread are frequently accessible because they are located on the skin or in regional lymph nodes. Additionally, metastatic disease generally has a fatal prognosis, and no effective treatments are currently available. Patients at high risk for disease spread after

the primary tumor is removed can be identified. Therefore, gene therapy can provide an additional treatment option for patients in clinical remission, as well as for those in advanced stages.

The goal of melanoma gene therapy is to treat systemic disease, not just local tumor growth. Approaches that enhance immune responses are better suited for this purpose because immune cells (CTLs) can move and attack tumors in various locations. In contrast, gene therapies using drug-sensitizing or corrective genes work only in local areas. Therefore, to achieve significant results, genes need to be targeted to all areas where tumors develop.

In melanoma gene therapy, the primary focus is on stimulating the immune response to attack melanoma cells. This strategy offers many advantages, including increased effectiveness on cells not directly exposed to the therapeutic gene. The ability of immune effector cells to migrate allows them to reach and destroy small remnants of cancer cells.

Several genes used in cancer gene therapy are those that play a role in inhibiting tumor growth. Tumor suppressor genes work by promoting apoptosis in cells that have become cancerous. These genes are often damaged in various types of cancer, so scientists aim to replace the damaged genes with normal ones.

Several cytokines exhibit immune activity against cancer when administered by injection into a vein or under the skin, such as interleukin-2, interleukin-12, alpha interferon, gamma interferon, and granulocyte-macrophage colony-stimulating factor. These cytokines have also been shown to be effective when injected directly into the cancerous area.

The genes encoding these various cytokines can be isolated. Introducing cytokine genes into cancer cells induces the cancer cells themselves to produce cytokines, thereby increasing antigen expression on the surface of the cancer cells. This allows the immune system to identify the cancer, which in turn triggers an immune response against both local and metastatic cancer. This approach has been well received and has shown success when compared to control groups in phase I/II clinical trials. In phase III clinical trials, direct injection of interleukin-2 or interferon-gamma genes into cancer sites is expected to yield response rates of around 15-20%, similar to the responses observed following systemic administration of cytokines.

GENE THERAPY

A relatively new approach in fighting cancer, known as immunotherapy, aims to stimulate the immune system to identify and destroy cancer cells while preserving the integrity of healthy cells. One of the most promising immunotherapy approaches involves using T cells that have been genetically modified to express chimeric antigen receptors (CAR) that can recognize tumor-associated antigens. The CRISPR-Cas9 system is an accurate and efficient gene-editing tool used to develop CAR-T cells with enhanced antitumor activity. Through CRISPR editing, T cells can be specifically tailored to improve their function and strengthen their ability to recognize and eliminate cancer cells.

Before reaching maturity and being released from the thymus, normal T cells must undergo a stage of positive selection. During this stage, thymocytes that recognize "self" antigens are eliminated through apoptosis, while thymocytes that recognize "non-self" antigens mature and migrate to the spleen or lymph nodes, where they encounter foreign antigens through major histocompatibility complex (MHC) presented by antigen-presenting cells. Additionally, activated T cells secrete cytokines such as IFN-gamma, TNF-alpha, and TNF-beta.

Unlike normal T cells, T cells with chimeric antigen receptors (CAR) are modified through viral or non-viral delivery methods to express recombinant genes for CAR, which consist of three domains: an extracellular domain with an antigen recognition region, a transmembrane domain, and an intracellular domain containing three immunoreceptor tyrosine-based activation motifs (ITAM), costimulatory molecules such as CD28, and an interleukin-12 (IL-12) domain that stimulates the innate immune system.

Due to CRISPR's capabilities as an effective gene-editing tool, impressive research has been conducted in gene knockout and knockin (KO/KI), providing various applications by replacing, adding, or deleting gene segments using sgRNA to achieve desired traits. For example, to address the issue of unwanted protein expression in cancer immunotherapy, steps are taken by designing single guide RNA, transferring gRNA and Cas9, followed by analyzing the results.

IMPACT OF GENE THERAPY

Although the development of universal allogeneic CAR-T cells is quite promising, several challenges still need to be addressed. These include developing streamlined protocols for delivering sgRNA and Cas9 while maintaining cell viability after genetic manipulation. Additionally, there are potential risks associated with using retroviruses, lentiviruses, and adeno-associated viruses (AAV) as viral vectors to deliver CRISPR-Cas9 components into cells. Another challenge of CRISPR-Cas9-mediated CAR-T cell editing is off-target effects and toxicity. Unintended editing can occur at non-target locations within the genome. These off-target effects can lead to undesired changes in gene expression, translocations, and large chromosomal aberrations, potentially causing toxicity and other side effects. Therefore, it is crucial to carefully design and validate CRISPR-Cas9-mediated editing to minimize the risk of off-target effects in CAR-T cells.

CONCLUSION

Based on the research conducted, it can be concluded that melanoma has properties that stimulate the immune system. Metastatic disease generally has a fatal prognosis, and no effective treatments are currently available. Patients at high risk for disease spread after the primary tumor is removed can be identified. Several genes used in cancer gene therapy are those that play a role in inhibiting tumor growth. Tumor suppressor genes work by promoting apoptosis in cells that have become cancerous. This approach has been well received and has shown success when compared to control groups in phase I/II clinical trials. In phase III clinical trials, direct injection of interleukin-2 or interferon-gamma

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