International Journal of Advanced Research in Medical, Nursing and Health Sciences ISSN: 2583-8474 (Online)
Volume – 2: Issue – 2 July – December - 2024

OVERCOMING RESISTANCE: STRATEGIES TO ENHANCE IMMUNOTHERAPY EFFICACY AGAINST CANCER

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Abstract:

There are several treatment strategies have been produced now a days to fight against cancer. From them treatment of cancer with immunotherapy and the use of the body's own immune system to attack and eliminate cancer cells has been proven worth it. Nevertheless, despite its positive effects on a few people, it has failed to work on many more due to resistance. Progressing with outcomes will require an understanding of why resistance occurs and how it may be checked. It is an obvious systemic approach for several diseases like different cancers including non-small cell lungs cancer (NSCLC), but most patients cannot withstand this because of primary or acquired resistance mechanisms. At the moment, clinical practitioners lack systems which may tell them that some patients are going to experience resistant development in immunotherapy hence causing treatment failures among other patients too. One possibility then arises: checkmate two targets simultaneously blocking their escape routes from immune surveillance could be regarded as an alternative way out when first-line strategies fail in restraining resistance's growth and providing effective second-line therapy.

Key Words: immunotherapy, immune system, biomarkers, non-small cell lungs cancer

Introduction:

Cancer could be a fatal illness, causing uncontrolled cell division which is called metastasis. Cell division in this kind of an individual is uncontrollable and is referred to as metastasis. Cancerous cells are able to invade, grow uncontrollably and metastasize simultaneously. It is possible to state that both stochastic and cancer stem cell models are characterized by some common peculiarities e.g., oncogenesis, driver mutations, tumour progression and metastasis. For example, diverse environments promote various traits for survival exhibited by cancer stem cells. Comprehensive models that integrate cancer and organism holistic techniques can fill these gaps. [1]

Cancer can be considered as an abnormal growth of cells inside an individual that has the capacity to invade and proliferate to other parts of the body which carries the disease by it but universally it takes millions to death yearly about ten were caused by it in 2020 alone and this resulted in almost 9,6 million deaths in the year 2018 alone, these were about 9,6 million people who died from cancer in 2018 alone. Given that cancer prevalence continues to increase globally, new methods of managing the disease are being sought [2].

Cancer may be a disorder that includes unusual cell development, with the potential to attack and disperse widely to the other parts of the body. It has gotten to be a very common cause of mortality, all inclusive, causing about 10 million mortalities in 2020. In 2018, around 9.6 million individuals passed away due to cancer. As the predominance of cancer proceeds to develop around the world, unused techniques are being sought for infection administration. Cancer could be a multifactorial illness, and different components such as excessive calories and way of life style, radiation exposure, and hormonal components can contribute to the advancement of this deadly illness. Way of lifestyle variables, such as smoking, liquor utilization, and dietary propensities, are considered to be critical contributing variables within the aetiology of cancer and are among the most important targets for essential avoidance. The conceivable association between eat less and the improvement of cancer cannot be neglected. Diets with high content red fat, such as processed and red meat, have been connected to development of colon cancers risk, though breast cancers have been associated with high-fat diets. Gene mutations within cancer cells transform them from normal cells into cancerous ones. These mutations can arise from inherited factors, accumulate over time due to aging and gene degradation, or occur due to exposure to genotoxic agents such as cigarette smoke, alcohol, or ultraviolet (UV) radiation from the sun [2,3,4,5].

Preserved, cured, or cured foods are associated with an increased risk of stomach cancers. Diets low in fibre and/or high in fat content are linked to cancers of the colon, prostate, pancreas, breast, endometrium, and ovaries. The clinical handling of cancer is determined by the nature and scope of the condition. Many individuals undergo a combination of therapies, such as surgical intervention in conjunction with chemotherapy and radiation treatment. Various alternative methods, including photodynamic and thermal therapy, immunotherapy, and genetic therapy, have also emerged as innovative cancer treatments. Phytochemicals are active compounds found in plants and are recognized for their antioxidant and anti-inflammatory

effects on the body. Among all the available phytochemicals, flavonoids and anthraquinones are known for their protective role against various types of cancers [5,6,7].

There exist unused treatment plans, including immunotherapy and accuracy pharmaceuticals which are now utilised for distinct purposes. All things considered; they are real benefits to the patients would be known as they were after the assessment of clinical information over next few years. In this manner, we got to see a few essential challenges that ought to be tended to in more depth some time recently. We might plan superior, thorough, and comprehensive treatment plans and may effectively reach a conceivable remedy for the infection [8].

Throughout history, cancer has been viewed as a cellular ailment, arising from genetic alterations dictating cell growth, specialization, and demise. Yet, in recent decades, attention has shifted to the microenvironment encircling cancerous cells, emerging as a conspirator in tumour inception, progression, evasion of immune response, and reaction to treatment. As tumours expand, they disturb the organization and function of nearby tissue through physical and biochemical means. These ensuing physical irregularities impact both cancer cells and their microenvironment, driving tumorigenesis and resistance to treatment. The intersections of cancer biology and physics have unveiled opportunities for uncovering new medications and treatment strategies [9].

Types of Cancer: There are several types of cancer but mainly distributed in five types. Those are, carcinoma, sarcoma, melanoma, lymphoma and leukaemia. Carcinoma generally diagnosed as a cancer which originate in breast, lungs, skin, Pancreas and other glands and organs. Sarcoma is relatively uncommon type of cancer and it generates in fats, blood vessels, bones, muscles, cartilage or other soft or connective tissues of body. Melanoma is a type of cancer which arises pigment in skin and affect the skin cells. Lymphomas are type of lymphatic or lymphocytic cancers. Leukaemia is the cancer of white blood cells and these are not form usually in solid tumours [10,11,12].

1. Breast Cancer: It Influences the breast tissue, transcendently in ladies but can also happen in men.
2. Lung Cancer: Affect the lungs and is happens due to regularly smoking, but can also happen in non-smokers due to other components like introduction to frequent smoke by

other people doing smoking, air pollution and radon gas which is invisible and doesn't have smell but its naturally occurs.

3. Prostate Cancer: Happens within the prostate gland in men and is one of the foremost common cancers in men with obesity, carcinogenic chemical exposure, family history etc.
4. Colorectal Cancer: Sedentary lifestyle, diet, smoking, excessive alcohol Influences the colon or rectum and ordinarily creates from polyps within the colon or rectum.
5. Skin Cancer: Occurs due to heavy sun exposure and radiation exposure from unusual skin cell development and incorporates sorts like basal cell carcinoma, squamous cell carcinoma, and melanoma.
6. Leukaemia: Influences the blood and bone marrow, driving to an overproduction of irregular white blood cells.
7. Lymphoma: A cancer of the lymphatic system, which incorporates lymph hubs, lymphatic vessels, and other lymphoid tissues.
8. Brain Cancer: Happens within the brain or central nervous system and can be primary (beginning within the brain) or metastatic (spreading from other parts of the body).
9. Pancreatic Cancer: Creates within the pancreas due to diabetes, pancreatic inflammation and is frequently analysed at a progressed arrange, making it troublesome to treat.
10. Ovarian Cancer: Influences the ovaries in ladies due to family history, changes in gene means inherited BRCA1, BRCA2 and is frequently analysed at an afterward stage, leading to a lower survival rate.

Causes of Cancer:

The fundamental abnormality under the Bonnet of cancer progression lies in the incessant unregulated multiplication of cancer cells. Whereas normal cells respond to signals that regulate their behaviour. cancer cells proliferate and multiply, invade normal tissues and organ, and finally Spill over to other parts of the body. This overall misfortune in the regulation of growth in cancer cells is the net result of accumulated deviations from the norm in the various cells behaviour that acknowledge cancer cells as their typical companions [12,13].

How to detect cancer:

Curing a cancer patient significantly depends on the proper diagnosis of diseases at primary stage. Tumours detected early, before they grow too large or spread, have a higher chance of successful treatment. Early cancer detection relies on several factors: screening at-risk populations, the ability of patients and healthcare professionals to recognize warning signs, and the use of diagnostic methods to distinguish cancer from other conditions and accurately determine the tumour location and extent.

- **Physically:** During a physical exam, your doctor may search for abnormalities, such as changes in skin colour or the enlargement of an organ, which could signal the presence of cancer. The doctor might also feel areas of your body to detect lumps that could indicate cancer. Typically, a health history is gathered alongside the physical exam. This health history includes a record of current symptoms, risk factors, and all past medical events and issues the person has experienced.
- **Pathologically:** Pathological diagnosis helps to detect cancerous or malignancy condition. In department of cytology with using a needle, the doctor extracts tissue or fluid, which is a technique often employed for bone marrow aspirations, spinal taps, and certain biopsies of the breast, prostate, and liver. In endoscopy, the physician called endoscope passed through a natural opening in the body, such as mouth or anus for removal of some or all abnormal tissues
- **Radiologically:** Medical pictures can be put into two groups: methods that show exact body parts and those that make functional or small particle pictures. The first method (using CT and MRI) can show tiny details about where and how big an abnormal spot is, what it looks like, and changes in nearby body stuff. But it can't say much about how the tumour works. The second method (using PET and SPECT) can give facts about how the tumour works, even down to tiny particles, but it doesn't show body details.

Understanding Cancer: Is it time for a new Approach?

Despite the vast amount of data accumulated through years of research, we still lack a comprehensive understanding of the underlying causes of these fatal conditions that result in millions of deaths annually, even with the advancements in science and technology. In truth, once cancers are recognized as traditional diseases, we must acknowledge that they could be seen as a complex result of ongoing changes at microscopic levels, impacting the entire physiology of the organism. We must acknowledge that the onset of the illness is not solely due to external factors or linked to the malfunction of a specific organ, unlike many other diseases.

Put simply, cancer can result from various malfunctions in the highly intricate cellular physiological systems. The beginning of the disease remains a mystery in the field of oncology, with a wealth of data pointing to different factors contributing to the transformation. However, surprisingly, all of these reports have led us to the edge of the iceberg. We need to gain a true understanding of when the illness begins in order to identify the proper targets for medication. Without this knowledge, we are unable to effectively treat the illness.

The last hundred years of logical investigation has provided us with a detailed understanding of primary, secondary, and tertiary changes linked to these conditions. Regardless, the pursuit of reaching point zero continues, and further efforts are necessary to achieve it at the onset of the infection. Raising the topic of the origin of cancer is important because our 'top-down' approach may be the main reason for our inability to decipher the codes of this long-standing problem and only providing relief for symptoms. Our focus has primarily been on developing and implementing strategies and procedures to capture the growth of altered tumour cell mass. Surprisingly, our focus has shifted mainly to creating modern preventive methods instead of investigating the underlying cause of the illness. Scientists have been consistently disappointed with the results of 'bottom-up' approaches in cancer research, which focus on cutting resources for cancer cells or activating cell death pathways. This has prompted the recent shift in focus towards understanding the origin of cancer. To comprehend the reasons and methods by which determination powers have allowed cancer-like conditions to become established within our current physiological ideal models, it is necessary to investigate the historical perspectives on the origins, nourishment, and progression of such ailments throughout history. In truth, we need a thorough multi-faceted strategy to effectively investigate and comprehend the infection in order to develop more successful treatment methods.

Although there have been advancements, there is still a lot of work left to do. Obstacles like resistance to treatment, cancer variations, and healthcare accessibility still present major challenges in effectively controlling and managing cancer. Furthermore, the increasing prevalence of specific cancers, the effects of aging populations, and the challenge of cancer in limited-resource areas highlight the necessity for ongoing investment and advancement in cancer research and treatment. Continuing studies seek to enhance immunotherapy's effectiveness, search for predictive biomarkers, and create combination treatments to overcome resistance and improve patient outcomes. The introduction of new immunotherapies has drastically transformed how genitourinary (GU) cancers are treated, becoming the main

approach in some cases. One type of immunotherapy, known as immune checkpoint inhibitors (ICIs) such as nivolumab, ipilimumab, pembrolizumab, and atezolizumab, actively enhance signalling pathways that suppress the immune system's ability to fight cancer cells. Despite the substantial impact of these medications, not every tumour will respond. Further investigation has focused on exploring how cancer cells evade the immune response and identifying the possible reasons for resistance to immunotherapy. As a response, ICIs are being mixed with other drugs to lower resistance and attack cancer cells via varying cellular pathways. Currently, there is a growing interest in exploring new methods to develop innovative strategies for overcoming resistance and treatment failures in novels [14].

Types of Cancer Therapies:

Cancer therapies are actually a group of treatments that aims to target the cancer cells and to ultimately benefit the patient. These consists of surgery, where the tumour is physically removed from the body; radiotherapy, using waves of very high energy to destroy the cancer cells; and chemotherapy where drugs are administrated to kill or slow their production. In addition, immunotherapy triggers the patient's immune system against the disease, and treated therapy identifies particular proteins that are involved in the generation of the disease.

Some cancers, like certain types of breast and prostate tumours, depend on hormones to grow; hence, hormone therapy may be used. Other newer approaches, namely personalized medicine and gene therapy, have given hope by using tailor made treatments based on the genetic make-up of a person, thus making them more efficient and less toxic [15].

- **Surgery:** Surgery plays a crucial role in cancer care, serving multiple purposes such as prevention, diagnosis, staging, and treatment. It can also alleviate discomfort or complications caused by cancer. In some instances, a single surgical procedure may address several of these objectives simultaneously, while in other situations, multiple surgeries might be required over time. Detailed information about specific surgical options can be found in the treatment guidelines for each type of cancer. As surgery is a common method to help diagnose cancer. Typically, the only definitive way to determine if someone has cancer and identify its type is by removing a small tissue sample and testing it. This diagnostic procedure, known as a biopsy, involves examining the cells under a microscope or conducting other laboratory tests. When biopsies are performed during surgery, they are often called surgical biopsies. The technique for

obtaining a sample varies depending on the tumour's location and the suspected type of cancer. For instance, prostate biopsies are performed differently than lung biopsies.

- **Targeted Therapy:** Targeted therapy encompasses a broad range of direct and indirect strategies. Direct approaches target tumour antigens for modification of their signalling, either by the use of monoclonal antibodies (MoAbs) or small molecule drugs that disrupt these target proteins. Indirect approaches take advantage of tumor antigens displayed on the surface of cells as targets for ligands carrying any variety of effector molecules. In these approaches, drugs can actively target tumours by means of tumour-specific MoAbs or peptide ligands that bind to receptors on the surface of the tumour cells. Apart from active targeting, the "enhanced permeability and retention effects" allow for tumours also to be passively targeted by macromolecules. which result from the leaky blood vessels and poor lymphatic drainage in tumours [16].
- **Chemotherapy:** Chemotherapy can be delivered through different methods. There are several common techniques that include: injection, oral, intravenous (IV administered directly into the cancer's blood supply, cream form of medication that can be applied topically on the skin, administered directly into the cancer's blood supply, Intraperitoneal (IP), Injecting a substance into the space between the layers of tissue surrounding the brain and spinal cord is known as intrathecal [17].
- **Immunotherapy:** The first known description of cancer is from an Egyptian papyrus from around 1600 BC. It was thus incurable until the nineteenth century, when anaesthesia, improved surgical techniques, and histological analysis were developed to make surgical removal more effective. Until 1950, surgery was used most frequently as a form of treatment. After 1960, radiation therapy became employed in controlling localised cancer. However, it became clear that neither surgery nor radiation, nor a combination of both, could adequately manage metastatic cancer. Effective treatment needed to target every organ in the body. As a result, modern cancer treatment focuses on drugs, biological molecules, and immune-based therapies [18].
- **Stem cell and bone marrow transplant:** The popularity of allogeneic and autologous bone marrow transplants is growing. BMT has now become a routine therapy for many patients with multiple myeloma, lymphoma, leukaemia, and testicular cancer. The treatment that was once referred to as bone marrow transplantation, or BMT, is increasingly being described today as hematopoietic stem cell transplantation. By 1990, E. The Nobel Prize in Medicine was awarded to Donnall Thomas and his team, thus

closing the early clinical era. Currently, hematopoietic stem cells are not obtained only from bone marrow but also from peripheral blood, as well as placental/umbilical cord blood. So the name has evolved from "bone marrow transplantation" to the more accurate "hematopoietic stem cell transplantation"[19].

- **Hormone Therapy:** Hormone therapy is remarkably effective and non-toxic for estrogenic receptor-positive and/or progesterone receptor-positive breast cancer and prostate cancer. Oestradiol, produced by the ovaries in premenopausal women, is derived from peripheral conversion of adrenal androgens by aromatase in postmenopausal women. The serum levels of both oestradiol and testosterone are regulated by the hypothalamic-pituitary-gonadal pathway. While in premenopausal women the ovaries produce oestradiol, in postmenopausal women, it is formed from a conversion of adrenal androgens through the activity of the enzyme aromatase. In the treatment of breast cancer in women before menopause and prostate cancer in men, castration is an important part of the therapy. Treatment for these patients often involves selective oestrogen receptor modulators, such as tamoxifen or aromatase inhibitors. Hormone therapy is a potential approach to reduce the size of the primary lesion before a decision to undergo radical surgery or radiotherapy and also to decrease the risk of recurrence. It has proven highly effective, particularly in patients with advanced local or metastatic disease, frequently resulting in an effective response. Despite early success, most patients quickly relapse, with their disease becoming "castration-refractory". Fortunately, a growing number of active agents are coming into clinical use to meet this challenge. [20].

Types of Immunotherapies:

Cancer cells and the immune system engage in complex interactions, sometimes providing protection against excessive cell growth, yet also potentially fostering malignancy. By grasping how the immune system safeguards against cancer, we can innovate novel therapeutic approaches. A variety of immunotherapeutic methods, such as adaptive cancer therapy, cancer peptide vaccines, monoclonal antibodies, and immune checkpoint inhibitors, have revolutionized the conventional cancer treatment paradigm [21].

- **Monoclonal Antibodies:** In a laboratory setting, monoclonal antibodies are crafted, distinct from the naturally occurring antibodies produced by the human body. These proteins serve the immune system by identifying disease-causing agents like bacteria

and viruses, tagging them for elimination. Much akin to the body's inherent antibodies, monoclonal antibodies are designed to pinpoint specific targets. Targeted cancer therapy, which involves the interaction with specific targets, encompasses many monoclonal antibodies utilized in cancer treatment. Over the past two decades, monoclonal antibody-based treatments have emerged as highly effective therapeutic approaches for both hematologic malignancies and solid tumours, marking significant success in cancer treatment [22].

- **Cytokines:** Cytokines act as molecular couriers facilitating communication among immune cells, orchestrating a unified, strong, yet controlled reaction to an antigen. While direct cell-to-cell contact is a common means of immune system communication, cytokine secretion expedites immune signalling, ensuring swift and effective coordination. Cytokines kickstart the action of immune cells and stromal cells right at the tumour site, making it easier for cytotoxic effector cells to identify and target tumour cells. Many studies using animal tumour models have shown that cytokines have a wide-ranging ability to fight tumours, leading to the development of several cytokine-based strategies for treating cancer [23].
- **Checkpoint Inhibitors:** The identification of the immune checkpoint proteins PD-1/PDL-1 and CTLA-4 represents a landmark discovery in the realm of cancer immunotherapy. As a result, humanized monoclonal antibodies that target these proteins have recently achieved unprecedentedly high efficacy in treating patients suffering from metastatic melanoma, renal cell carcinoma, head and neck cancers, and non-small cell lung cancer [24].
- **Vaccines to treat cancer:** Vaccinating to prevent infectious diseases is widely acknowledged as one of the most effective health strategies ever. But using vaccines to treat established diseases like chronic infections and cancer is a tougher nut to crack. This is because the immune system, which has been held back by mechanisms aiming for self-tolerance, poses a significant challenge. Nonetheless, recent clinical trials show that we're making strides toward successful therapeutic vaccination [25].
- **CAR T-cell therapy:** CARs, specialized receptors designed to target a specific tumour antigen, are crafted to alter the behaviour of T lymphocytes. Genetically modified T lymphocytes carry these engineered receptors, empowering them to seek out cancer cells. This strategy falls under the categories of immunotherapy, gene therapy, or cancer

treatment. Our immune system excels at discerning between self and non-self-entities, including bacteria, viruses, and aberrant cancer cells [26].

Understanding Resistance Mechanisms:

The goal of each cancer therapy is to eliminate the disease and achieve full recovery. Even with notable progress in treating some types of cancer, numerous patients continue to have difficulty responding well to treatments. Various internal and external factors may disrupt the body's innate reaction to cancer therapies, leading to resistance. This resistance can be classified into three categories—primary, adaptive, and acquired—depending on when it emerges in the treatment process. Over the last ten years, there have been notable developments in immunotherapy for the treatment of B-ALL. Both treatment options utilizing antibodies or cells have demonstrated potential, enabling patients diagnosed with relapsed and refractory B-ALL to achieve a state of remission. Still, only a small number of patients attain a permanent cure. This chapter analyses the obstacles to long-term success in immunotherapy and explores methods to improve the longevity of remissions. Immunotherapy might not be effective because leukaemia cells have inherent characteristics that make them resistant to treatment, or because the immune system has difficulty maintaining the disease in remission [27].

The relationship between cancer and immunotherapy:

Immunotherapy is currently a widely used treatment for various cancers and has revolutionized our approach to combating the disease. ICIs have demonstrated effectiveness in treating different types of solid tumours such as melanoma, RCC, NSCLC, and colorectal cancer with mismatch-repair deficiency. These immune checkpoint inhibitors function by disrupting the communication between inhibitory receptors on T-cells and their corresponding ligands on cancerous or myeloid cells, initiating the immune system's response to tumour-specific antigens [28].

Future Perspectives:

Despite the significant stride made by different treatment modalities, the brutal reality still remains that the "war on cancer" is still an ongoing affair. Serious challenges still persist with FDA-approved drugs available nowadays including constraints related to the inherent resistance and acquired resistance mechanism of monoclonal antibodies, which are contributory in mediating tumour heterogeneity and patient relapse [29].

Such different types of immunotherapy-based strategies have, within the past few years, successfully transformed the way treatment is administered for a number of other forms of cancers. The immune response now enhances anticancer activity through immune checkpoint inhibitors, CAR-modified T cells, dendritic cell-based therapies, NK-CAR T cells, and CRISPR-Cas9 technology. These developments have shown the wide utility and adequacy of different helpful methodologies in immunotherapy to battle disease [30].

With the approach of immunotherapy for malignant growth, the future heading of cancer therapy is supposed to be a time in which need is given to treatments pointed toward relieving malignant growth, as opposed to choosing treatments that are supposed to delay patients' lives as previously. Disease immunotherapy up to now has zeroed in on the most proficient method to productively actuate and improve the safe reaction to malignant growth.

Since the mechanisms of action in cancer immunotherapy differ fundamentally from those of traditional cancer drugs, treatment strategies must be devised with a thorough understanding of these unique characteristics. In particular, combination therapies involving immune checkpoint inhibitors hold significant promise for future advancements. Employing these inhibitors with a comprehensive understanding of each drug's properties can result in not only additive but also synergistic effects.

Currently, more than 2,500 clinical trials for combining cancer immunotherapy with immune checkpoint inhibitors are actively ongoing, with the hope of increasing therapeutic efficacy. Another new cancer immunotherapy, CAR gene transfer T-cell therapy, has been approved for the treatment of B-cell hematopoietic malignancies. [31].

Conclusion:

Moreover, most recent data also indicate that many other novel targeted therapies are likely to have immunomodulatory effects. Therefore, even though the future may be bright with further improvements in clinical outcomes and potential cure of most cancers with combination immunotherapy strategies, with or without targeted therapies, similar to how combination chemotherapy has proved to be better than single-agent therapies for most of these diseases, much is yet to be worked on to ensure the full benefits of its application are indeed reaped. However, development of good robust predictive biomarkers that are able to accurately assess determinants of tumour immune responsiveness will be pivotal in guiding the development and

personalize combination of strategic immunotherapy. Personalized cancer immunotherapy is going to result in improved efficacy, reduced toxicity, and reduced cost of treatment [32].

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