Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

Therapeutic Approaches to Immunotherapy Induced Chronic Inflammatory Diseases

Emmanuel Adebola Adebanjo[1] , Kafayat Motomori Bakare[2], Ugochukwu Okwudili Matthew[3], Lateef Olawale Fatai[4] , Anyigbo Ujunwa Precious[5]

[1,2]Public Health (MPH), University of New Haven, USA.
[3]Computer Science Department, Hussaini Adamu Federal Polytechnic, Nigeria.
[4]Data Science, University of Salford , United Kingdom.
[5]Microbiology Department, Federal Polytechnic Oko, Nigeria.

Abstract

The development of immunotherapy vaccines hinges on the identification of suitable biomarkers and the optimization of treatment combinations to enhance their efficacy in patients. Over the past few decades, research on immunotherapy vaccines has advanced, leading to the availability of numerous defined vaccinations. Still unsolved are a few issues, such as appropriate tumor antigen, adjuvant components for chronic inflammatory diseases, appropriate delivery mechanisms, and efficient strategies to fend off immunological attacks. The term chronic inflammatory diseases (CID) refers to a group of illnesses in which the immune system is unable to control typical acute inflammation, resulting in an ongoing, unresolved state of inflammation. Conditions including psoriasis, inflammatory bowel disease, and rheumatoid arthritis affect a considerable number of people globally, making the CID a substantial burden on global healthcare systems. Conventional therapies frequently relieve symptoms, but they may also have serious adverse effects and be ineffective. By focusing on the dysregulated immune responses that underlie chronic inflammatory illnesses, immunotherapy has become a viable treatment option. With a focus on important therapeutic approaches, mechanisms of action, clinical efficacy, and safety profiles, this research paper offers an extensive assessment of immunotherapy-induced treatments for chronic inflammatory illnesses. Furthermore, the paper addresses the present CID conundrums and potential paths forward in the creation and enhancement of immunotherapeutic treatments for the crippling ailments.

Keyword: Immunotherapy, Chronic Inflammatory Diseases (CID), Immune-mediated inflammatory disorders (IMIDs), Cancer Treatment, Clinical Oncology

1. INTRODUCTION

Global mortality and morbidity statistics are greatly impacted by chronic inflammatory diseases(CID) as well as a number of other conditions with underlying pathology connected to chronic inflammations(Harris et al., 2024). Anti-inflammatory medications that are now in the market have significant drawbacks, including severe side effects and exorbitant treatment costs, despite their demonstrated effectiveness. Since natural products have a distinct chemical variety, they offer good substitutes for these medications and may help identify new lead compounds for

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

the development of pharmaceuticals to treat inflammatory illnesses. This paper presented basic research on natural products' activities against inflammatory illnesses as well as noteworthy studies on natural products with anti-inflammatory properties. There are many different types of immune-mediated inflammatory disorders. Over the past 20 years, the therapeutic arsenal for immune-mediated inflammatory illnesses has changed, despite the fact that they are now incurable(McInnes & Gravallese, 2021). Due to advancements in monoclonal and molecular biotechnology, as well as more recently, highly targeted medicinal chemistry, we have transitioned from the widespread use of broad-spectrum immune modulators to the routine use of medicines with precise specificity. Here, we outline the significant developments and insights that propelled this amazing advancement and then consider the next steps in this continuous process.

Furthermore, a number of co-morbidities, including as cognitive impairment, metabolic and bone problems, and cardiovascular disease, are frequently present with these diseases, which negatively affects mortality and quality of life even more(Parren et al., 2015). Since these provide a striking illustration of the advancements made in targeted illness therapy, we mainly concentrate on immune-mediated and autoimmune rheumatic disorders here. Immune-mediated inflammatory disorders (IMIDs) have seen a transformation in the last 20 years in terms of the therapeutic arsenal. The widespread use of broad-spectrum immune modulators has given way to the routine use of highly specific medicines, which are the result of advancements in molecular and monoclonal biotechnology, as well as the more recent use of highly targeted medicinal chemistry. We also consider the future steps in this amazing journey, and we outline the major discoveries and lessons that fueled the creation of innovative immune-targeted medicines. By the end of the 20th century, glucocorticoids and a host of other tiny chemicals—many of which were taken from other fields—became crucial to IMID therapy because of their impact on cell metabolism or antiproliferative properties. Glucocorticoids were the cornerstone of treatment for a number of IMIDs starting in the 1940s. Despite their versatility and efficacy, they showed significant toxicity to bone, cardiovascular systems, and metabolic function over time, as well as a declining therapeutic benefit(Williams et al., 2023).

The use of other mainstay therapeutics included methotrexate, azathioprine, sulfasalazine, hydroxychloroquine, D-penicillamine, and mycophenolate; however, the clinical application of these drugs was rarely adequately defined in terms of immune specificity or, in fact, in terms of the underlying pathogenesis of disease(Kutija, 2023). Because there was a high risk of adverse events, these agents were employed one after the other or in combination with extreme caution. Clinical outcomes were, by today's standards, at best, with a high prevalence of non-responder and partial responder populations and a low rate of remission. Sadly, for most IMIDs, long-term impairment was the expected norm(McInnes & Gravallese, 2021).
A changed landscape was foreshadowed by two important achievements. With the introduction of cytokine blocking and the ground-breaking use of tumour necrosis factor (TNF) inhibitors in the treatment of rheumatoid arthritis (RA), a new paradigm of biotherapeutic innovation based on

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

important pathogenic disease mechanisms was established(Parren et al., 2015). Fast changes resulted from this, including the introduction of biological and, more recently, small-molecule-based immune-targeted therapies that target a variety of cytokines and their receptors, inflammatory cell trafficking pathways, cell regulatory ligand pairs, and the use of cell depletion tactics. Accompanying this growing variety of biological and small-molecule treatments was another important development: the understanding that tight regulation of inflammation is essential to the course of disease(Li, Hadi, & Guttman-Yassky, 2019).

Thus, the clinical approach to managing IMID underwent significant strategic changes. Early diagnosis and intervention were given more importance, and the aim was to achieve remission or low disease activity states while preventing damage to target organs and thereby improving longevity and quality of life. Non-steroidal anti-inflammatory medications (NSAIDs) and corticosteroids are used in current therapy. Methotrexate and cyclosporine have been utilized more recently. When used in conjunction with ultraviolet light therapy (PUVA), photo chemotherapy is frequently an effective treatment method. These therapies are definitely not disease-specific and can have a wide range of adverse effects in addition to variable effectiveness rates. Methotrexate is a useful alternative, especially in cases with lichen planus, although it is often necessary to quit treatment due to adverse effects, and liver function must be closely monitored. When combined with the photosensitizing medication psoralen, ultraviolet A therapy (PUVA) can be beneficial, but as with other sun-sensitive or fair-skinned people, negative effects might occur, such as cataracts and skin cancer(Matthew et al., 2022).

While Ultraviolet B (UVB) is useful in removing lichen planus lesions, prolonged exposure to it damages skin further and raises the risk of skin cancer(Mahajan, Kokare, Raut, & Itankar, 2022). It is impossible to declare any of these treatments to be specific, safe, effective, or well tolerated. Thus, it would be better if future research focused on developing targeted, less hazardous treatments or a cure for skin conditions like lichen planus. The adverse effects and permanent incapacity caused by the medications now in use are not acceptable. Chronic inflammatory illnesses are difficult to cure and can lead to a lower quality of life for the patient. The absence of healing and increasing tissue deterioration are typical characteristics of these disorders. Further tissue deterioration results from the laying down of a fresh set of chronic inflammatory lesions. This is undoubtedly the case for lichen planus, the model selected to contrast with the etiology of inflammatory illnesses like rheumatoid arthritis. T-helper 2 (Th2) cell-driven autoimmunity is well supported by the available data, while Th1 immunity-inducing therapeutic approaches are working well in animal models of autoimmune disorders. But trying to change the immune response of a chronic illness that has already developed could backfire. When cytotoxic chemicals are being used to target cancer, autoimmune illness that was first brought on by chemotherapy is likely to make Th1 type inflammation worse.

While immunotherapies that increase the immune system's capacity to target cancer cells have promise for treating a variety of tumor types, individual patient responses to these treatments

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

vary. Novel approaches to cancer immunotherapy that target T cell-mediated anti-tumor responses have garnered more attention recently. T lymphocyte-mediated antigen-directed cytotoxicity has emerged as a key player in the immune system-based fight against cancer. Novel therapeutic techniques in cancer immunotherapy, such as checkpoint blocking, adoptive and chimeric antigen receptor (CAR) T cell therapy, and cancer vaccine research, have been guided by the molecular and cellular mechanisms underlying T lymphocyte activity(Ahmed et al., 2023). When cancer cells perish, they release compounds known as antigens, which the immune system can identify. Antigen-presenting cells (APCs) are unique immune cells that take up and present antigens from cancer cells on their cell surface, allowing other immune cells to "see" the relevant antigens. The T-cells in the lymph nodes are trained to identify tumor cells by the APCs(Liang, Cheng, Liu, & Liu, 2022). The blood arteries are subsequently used by the T-cells to enter the tumor, penetrate it, and identify the cancerous cells.

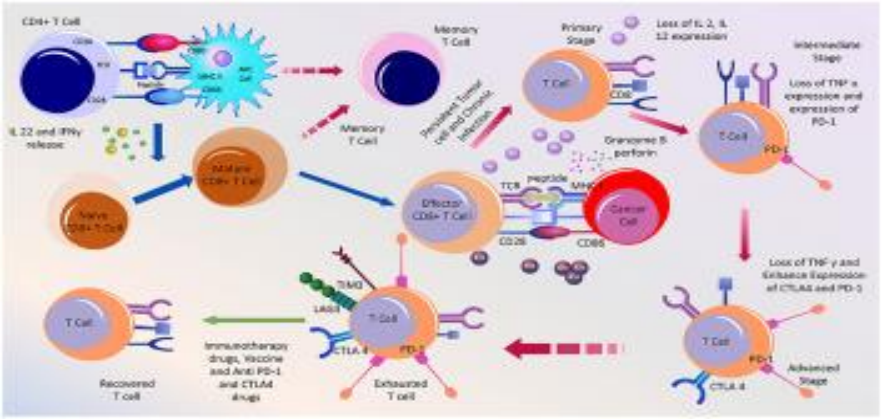

Figure 1: T cell involvement in cancer immunotherapy(Ahmed et al., 2023).

Immunotherapy-induced inflammation may worsen autoimmune disease and make patients more prone to relapse frequently if attempts to treat it fail(Nabel et al., 2019). Eliminating cancer cells while preventing the worsening of pre-existing autoimmune illness would be a better result(Haanen et al., 2020). If a cancer-specific immunotherapy could be given in a way that avoids systemic inflammation, then this may be possible. By 2030, the incidence of cancer is predicted to rise by 72% globally(Z. Liu et al., 2021). Food allergies are becoming more common by 4-6% year, with prevalence rates reaching 7-9% in Western countries(Warren, Jiang, & Gupta, 2020). Furthermore, there is a sharp rise in the occurrence of autoimmune diseases. Up to 5% of people in the West suffer from chronic autoimmune illnesses, and this number is rising quickly. Even while these numbers are concerning, increased research and scientific progress have resulted from them, in part because these diseases are now more widely recognized and diagnosed. It is currently anticipated that autoimmune diseases, food allergies, and cancer prevalence rates would continue to rise. Patients who are undergoing cancer therapy, especially those receiving chemotherapy, may develop autoimmune illness(Fountzilas et al., 2022).

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

2. Research Purpose

This study examines new approaches that target tumor pathogenesis, such as metabolic pathways, in order to assess the clinical significance of immunotherapies now and in the future for cancer patients. These treatments also involve T cell activation, tumor differentiation response, and inflammatory diseases. Since the methods for studying, which involve cellular and molecular processes, have advanced so quickly, our understanding of chronic inflammatory illnesses is today both more concentrated and sophisticated than it was in the past. The genesis of this concept is well recognized because it is well established that immunopathologic characteristics in inflammatory tissues and the immune system are intimately related to chronic inflammatory disease. The immune system and inflammation are intimately related, despite the fact that this relationship is currently poorly understood. This means that when a stimulus is removed, the immune system reacts, but tissue regeneration and normal function frequently follow.

This work aims to provide an overview and summary of the current understanding on the management of chronic inflammatory diseases generated by immunotherapy. An acute, protracted, and continuously progressing process that can impact an individual or the entire organism, chronic inflammatory illness results in a series of histological, morphological, and functional alterations, as the body undergoes these modifications concurrently with an attempt to eliminate the damage-causing agent.

3. Current Treatment Options to Immunotherapy Induced Chronic Inflammatory Diseases

The advent of immunotherapy in the past 20 years has offered cancer patients fresh hope as it has proven to be a successful alternative treatment option for a variety of malignancies(Kamrani et al., 2023). Immunotherapy is well known to stimulate the immune system's ability to fight cancer, and it frequently has immunological adverse effects. Dermatologists routinely treat a variety of inflammatory skin disorders that arise with anti-cancer therapy. These are frequently severe enough to change the dosage or result in the cessation of potentially life-extending treatments. It is still difficult to handle adverse effects associated with cancer immunotherapy because of the variety of clinical manifestations and the lack of knowledge regarding the etiology. Treatments for immuno-oncology-induced inflammatory disorders are necessary because stopping the causing anti-cancer treatment will sometimes relieve the symptoms, but this is not always desirable(Wang, Ma, Lin, Wang, & Cao, 2024). With the growing use of immunotherapy, dermatologists and perhaps other medical professionals will need to learn more about these reactions in order to recognize and manage this new class of immune-related side effects. Since the field is very young, the theory is that undesirable events related to the internal immune system may be more severe and can be seen via the skin. The possibility that effective therapies for inflammatory diseases specific to the skin that are caused by immuno-oncology may

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

also have the advantage of promoting tumor immunity is therefore quite exciting(Taylor, Gandhi, Gray, & Zaenker, 2023).

This relates to the idea of immunostimulation for the benefit of cancer patients who are receiving assistance; an increase in immunity has the potential to prolong longevity and even cure an undiagnosed subclinical tumor. Further investigation is warranted in this area, and hence, therapies targeting inflammatory disorders caused by immuno-oncology may have implications for the broader field of cancer therapy. An essential mechanism by which the immune system recognizes and eradicates developing tumor cells is cancer immune surveillance. Tumor-associated antigens (TAAs) allow the immune system to identify and destroy tumor cells when they infiltrate healthy tissue. Tumor cells can, however, avoid the immune system by employing a number of strategies known as immunological escape. There are four primary mechanisms: 1) suppressing T-cell activity by upregulating immune checkpoints on the surface; 2) lowering immunogenicity by downregulating surface antigen expression; 3) enlisting suppressor immune cells, such as regulatory T cells (TReg) and myeloid-derived suppressor cells (MDSCs), along with cytokines, to form a suppressive immune microenvironment; 4) releasing toxic and acidic metabolites that prevent immune cells from acting in the tumor microenvironment. After heart and stroke disorders, cancer is the second most common cause of mortality in humans, and its patient base is steadily growing. Immunotherapy is the latest advancement in cancer treatment, following surgical resection, radiation therapy, chemotherapy, and targeted medication therapy. Through the production of anticancer effects, cancer immunotherapy reactivates the immune system of the body, killing and eliminating malignant cells(Wu, Li, & Zhu, 2021). One promising treatment is immunotherapy. In contrast to conventional treatment, immunotherapy modifies the tumor microenvironment by using certain cytokines, chemokines, and immune cells. This can have significant effects and stop recurrence.

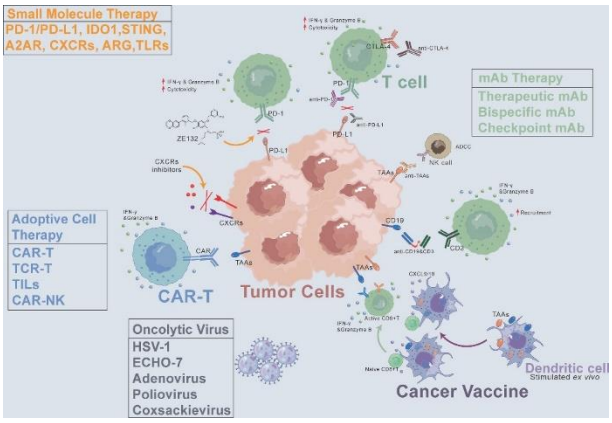

Figure 2: Techniques for cancer immunotherapy include oncolytic viruses, adoptive cell therapy, small molecule medications, monoclonal antibodies (mAbs), and cancer vaccines. Chimeric antigen receptor, or CAR. C-X-C motif chemokine receptor, or CXCR. Tumor-associated

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

antigens, or TAAs. antigen-dependent cell-mediated cytotoxicity, or ADCC. Programmable death-1 (PD-1) and Programmable death-ligand 1 (PD-L1). Cytotoxic T-lymphocyte-associated protein is known as CTLA-4(Alard et al., 2020).

The paradigm for treating tumors has shifted with the development of immunotherapy. The most recent developments in cancer immunotherapy are covered in this article, including adoptive cell treatment, small molecule medications, oncolytic viruses, monoclonal antibodies (mAbs), and cancer vaccines refer to figure 2. In this review, we address immunological resistance, limits, and combination tactics in an attempt to provide a positive perspective for the advancement of cancer immunotherapy in the future.

4. Preventive Immunotherapy for cancer Treatment

Preventative cancer vaccines have made greater progress in preventing cancer than in removing established cancer; the immunological prevention of cancer and cancer recurrence has attracted a great deal of research(C. Liu, Yang, Zhang, Chen, & Zhu, 2022). However, it is evident that preventing cancers affects survival. In general, vaccinations against viruses with a high carcinogenic relevance are referred to as preventive cancer vaccines. Vaccines against Human Papillomavirus (HPV) as primary examples. There are currently several novel HBV vaccines available that increase the effectiveness and range of protection, including Hepacare, HEPLISAV-B, and PreHevbrio(C. Liu et al., 2022). In order to protect against HPV-related cervical, vaginal, and vulvar cancer, the three major HPV vaccines are bivalent and nine-valent. This technique is limited to usage as a supplemental preventive measure because to the intricate pathophysiology of malignancies. Not tumorigenesis, but simply viral infection prevention is possible with this kind of vaccination.

5. Therapeutic cancer vaccines

The evolution of the natural immune response, novel antigen delivery technologies, and a deeper comprehension of the range of TAAs will all contribute to better vaccine design. The dendritic cell (DC) vaccine is one of the most developed therapeutic vaccines available today. It works against cancer by stimulating the patient's monocytes to develop into DCs by TAA stimulation(Najafi & Mortezaee, 2023). After that, the patient receives another infusion of the cells to promote the growth and activation of cytotoxic T lymphocytes (CTLs). Long-term immunological memory and tumor recurrence prevention are two benefits of the DC vaccination.

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

Name	Company	Highest Development Phases
Provenge	Dendreon	Marketed (FDA)
Cimavax-EGF	Bioven	Marketed (Cuba)
Mutanome	BioNTech	Phase I (NCT04183166)
NEO-PV-01	Neon Therapeutics	Phase I (NCT02897765)
AV-GBM-1	Aivita Biomedical	Phase II (NCT03400917)
TEDOPI	OSE Immunotherapeutics Bristol-Myers Squibb	Orphan Drug (HLA-A2 NSCLC)
Ilixadencel	Immunicum	Orphan Drug (Soft tissue sarcoma)

Table 1: Investigational cancer vaccine research progress(C. Liu et al., 2022).

An increasing number of tumor antigens that can be utilized to differentiate tumor cells from normal cells have been found thanks to advancements in sequencing technology and bioinformatics. Such a tailored vaccination design is a significant future direction for cancer vaccine research and development. According to numerous research, tailored vaccinations are effective in treating melanoma. Using immunological checkpoints in combination is a promising area of study that has the potential to outperform individual vaccination therapies. Tumor cell, DNA/mRNA, and peptide vaccines are examples of therapeutic vaccinations in addition to DC vaccines. Long preparation times, expensive, and scarce cell sources are the drawbacks of DC vaccines. They still have a wide market potential, nevertheless, because of their benefits, which include minimal adverse effects, high tolerance, and long-term immune memory. Understanding which biomarkers to look for and how best to combine treatments to increase patient efficacy will be crucial to developing a cancer vaccine. A multitude of defined cancer vaccines are currently on the market as a result of decades of advancements in vaccination research. Appropriate tumor antigen and adjuvant components, appropriate administration modalities, and efficient strategies to fend off immune response are some of the issues that still need to be resolved. While neoantigens represent the gold standard for antitumor immunotherapy, the challenge of producing customized neoantigens impedes the development of cancer vaccines. The primary causes of this are the development of an immunosuppressive TIME and intrinsic changes in tumor cells. Numerous strategies have been devised to get over obstacles, such as combining ACT and ICB with immunostimulatory adjuvants.

6. Potential Advances in Cancer Immunotherapy Treatment

Immunotherapy for cancer patients, such as adoptive cell therapy (ACT) and immunological checkpoint blockade (ICB), is beneficial(Lee & Kim, 2023). However, a variety of immune-resistant mechanisms and the absence of immunogenic antigens continue to restrict the response rate of cancer immunotherapies. Improving the effectiveness of the available cancer immunotherapies requires an understanding of the immune resistance mechanisms. Individuals

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

who do not respond to the first treatment are said to have primary resistance to cancer immunotherapies. The immune system's ability to identify tumor cells is known as "adaptive resistance," and as the tumor grows, it can adjust to immune attack in order to defend itself. Primary resistance may be a component of the adaptive resistance mechanism or the outcome of the adaptive resistance mechanism. Tumor antigen deficiency is the primary cause of tumor cell non-reactivity to immunotherapy, as tumor cells are not identified by T lymphocytes. Tumor antigens may also be present in cancer cells, although immune resistance may also arise from modifications in the antigen presentation pathway(Jhunjhunwala, Hammer, & Delamarre, 2021).

Primary and adaptive resistance in tumor cell-intrinsic factors are influenced by neoantigens and insufficient tumor antigenicity. Through the downregulation of Tumor-associated antigens(TAA), Tumor-specific antigens(TSA), and surface histocompatibility complex (MHC) expression, tumor cells can avoid being recognized by T cells as part of a specific immune response(Janelle, Rulleau, Del Testa, Carli, & Delisle, 2020). Relatively poor immunogenicity allows tumor cells to evade immune system surveillance and multiply only in specific directions. Following the process of immune selection, the tumor's immunogenicity becomes weaker. Neoantigen formation can impede the growth of cancers, but tumors with low immunogenicity are not affected by PD-1/PD-L1 blocking. Primary resistance to immunotherapy in triple-negative breast cancer (TNBC) is caused by neoantigen deletion. The infiltration of cytotoxic T lymphocytes in tumor necrosis fields (TNB) is negatively correlated with LINK-A, a lncRNA that can degrade phospholipase C by ubiquitin ligases. Presently held beliefs indicate that a greater T cell response and increased production of neoantigens are associated with higher tumor mutation burdens (TMB). Clinically, low TMB prostate and pancreatic cancer respond less well to anti-PD-1 therapy than high TMB melanoma, renal cell carcinoma, and non-small cell lung cancer.

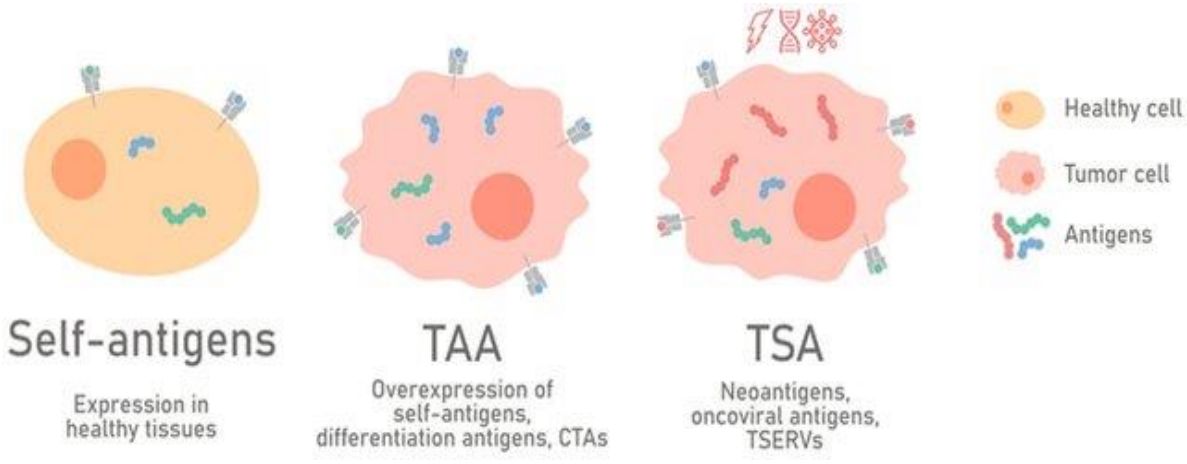

Figure 3: Tumor antigen classification. Tumor-associated antigens and tumor-specific antigens (are two general categories of tumor antigens that are determined by the parental gene's expression pattern.(Janelle et al., 2020) These are self-proteins called TAAs that are expressed in cancer cells.

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

When cancer cells transform malignantly, these proteins can overexpress normal genes (gene overexpressed), express proteins with tissue-specific gene patterns (differentiation antigens), or express proteins that are derived from gene expression that is limited to the testes (cancer germline/cancer testis antigens). Tumor-specific endogenous retroviruses (TSERVs), oncoviral antigens, or mutations can all result in TSAs, which are proteins expressed by tumor cells. They can also be caused by viruses participating in the oncogenic transformation.

7. Combinatorial approaches in cancer immunotherapy

When combined with immunomodulatory strategies that can positively modify the TME with the goal of counterbalancing the severe immune suppressive environment, the efficacy of immunotherapies in Hepatocellular carcinoma (HCC) can be greatly increased(Hou, Zhang, Sun, & Karin, 2020). Although maximum tolerable dose (MTD) and low-dose metronomic chemotherapy are thought to depress the immune system, they may actually strengthen antitumor immunity through a variety of pathways. Specifically, a number of studies have shown that immune-suppressive cell populations—such as MDSCs and Tregs—can be specifically eliminated. Additionally, cancer cells can be made to undergo immunogenic cell death (ICD) by releasing danger signals that can polarize DCs and trigger an anti-tumor T helper 1 (Th1) response. Additionally, they have the ability to alter the expression of immune checkpoint molecules and tumor antigens, changing the TME and enhancing the effectiveness of immunotherapy treatments. When surgical procedures are not appropriate for treating early-stage HCC patients, radiofrequency ablation (RFA) is thought to be the first line of treatment. RFA causes tumor death by inducing necrosis and apoptosis in the tumor. Both the release of neoantigens and TAAs causes a considerable intratumoral immune infiltration and immune response activation. Due to the aforementioned factors, immunomodulatory therapies have the potential to greatly enhance the effectiveness of anticancer immune responses brought on by cancer vaccinations.

Nowadays, combination therapy has been a popular area of research to improve the efficacy of cancer immunotherapy and overcome immunotherapy resistance. In clinical combinations, ICB is the most commonly utilized cancer immunotherapy at the moment. Combining anti-CTLA-4 with anti-PD-1 therapy has been shown to be more effective, as evidenced by increased response rates and improved survival rates in melanoma patients. The combination group (nivolumab plus ipilimumab) achieved a five-year survival rate of 52% in the phase III trial, while the individual groups' respective five-year survival rates were 44% and 26% for patients with unresectable or metastatic melanoma. Furthermore, blocking TIM-3, LAG-3, and TIGIT is becoming more and more important(Cai, Li, Tan, Xu, & Li, 2023). It was discovered that inhibiting TIM-3 and PD-1 together can totally reverse the tired condition of T lymphocytes and has a major anticancer effect in the treatment of hepatocellular carcinoma. Nevertheless, T cell function was only partially recovered by PD-1 or TIM-3 inhibition alone. Blocking both LAG3 and PD-1 can have an immunological synergistic impact by improving CD8+ T cell activity and

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

eliminating Treg(Van Damme et al., 2021). Both LAG3 and PD-1 can communicate co-inhibitory signals. The immunosuppressive signal is mediated by TIGIT, which is mostly expressed on activated T cells and natural killer cells. TIGIT inhibition and anti-PD-1 work together to improve CD8+ T cell activity and accelerate tumor shrinkage.

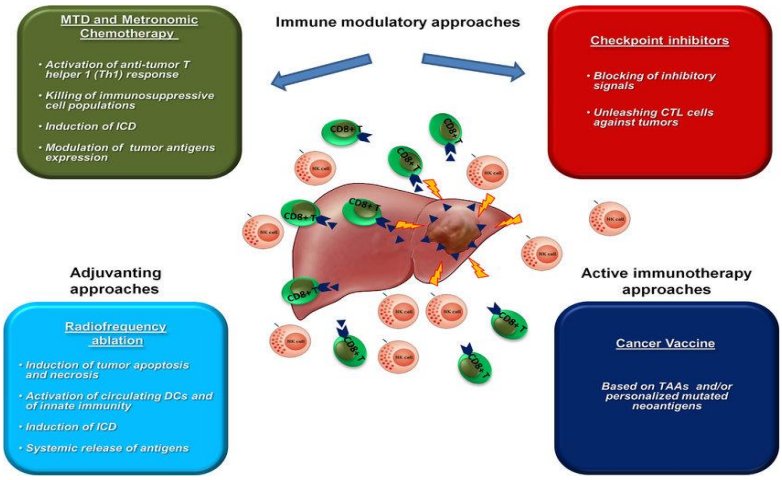

Figure 4: Combinatorial method for treating Hepatocellular carcinoma (HCC). The immunological therapies for HCC that are now available are displayed. It is anticipated that using both of these together will significantly improve clinical outcomes for HCC patients(Kole et al., 2020).

8. Synergized chemotherapy and radiotherapy

Chemotherapy was formerly thought to cause immunosuppression by influencing the quantity or quality of lymphocytes(Mukherjee, Rakshit, Shanmugam, & Sarkar, 2023). However, comprehensive research has shown that certain chemotherapy regimens can increase tumor immunogenicity. Chemotherapy has been shown in certain trials to improve the antitumor immune response; the FDA has approved the use of pembrolizumab in conjunction with chemotherapy. In mice, liposome doxorubicin with immunotherapy has synergistic anticancer benefits; more mice experience total tumor remission and longer life times. Chemotherapy administered often and at modest doses can efficiently stimulate CTLs and reduce immunosuppressive cells in TIME, hence enhancing efficacy and resolving the immunological resistance issue. When oxaliplatin was used with an in-situ CRC-bearing mice model that was not responding well to anti-PD-L1 therapy, the percentage of TILs increased dramatically. Simultaneously, oxaliplatin and a new PD-L1 inhibitor (PD-L1 Trap) markedly increased the longevity of tumor-bearing animals. For advanced non-small cell lung cancer (NSCLC), chemotherapy plus anti-PD-1 is utilized as a first-line treatment, which has far greater therapeutic advantages than chemotherapy alone.

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

In order to increase the immunogenicity of tumor cells and facilitate the recruitment and infiltration of immune cells, radiotherapy induces the production of TAAs, TSAs, or damage associated molecular pattern molecules(Kumari et al., 2020). Combining immunotherapies makes sense in light of this link. Combining anti-PD-1 medication with radiation reduced immunological resistance in a mouse model research. Radiation therapy in conjunction with anti-CTLA-4 and anti-PD-1 therapy may be a novel concept in combination immunotherapies for the treatment of metastatic melanoma. In a mouse model of breast cancer, Pilones et al. found that anti-CTLA-4 in conjunction with radiation therapy successfully prevented lung metastases(Pilones, Vanpouille-Box, & Demaria, 2015). It was discovered by Deselm et al., that in a mouse model of pancreatic cancer, radiation increased the effectiveness of CAR-T cells, and that CAR-T cells also killed tumor cells that did not express the CAR target(Hauth, Ho, Ferrone, & Duda, 2021).

9. Discussion of Research Findings

The onset and progression of cancer are intricate processes that impact bodily tissues and cells. The body's immune response, which gets increasingly intricate as cancer spreads, can be countered by a variety of immune-evasion techniques(Bakare, Nkeiruka, Matthew, Ebong, & Oyekunle, 2024). After targeted therapy, radiation, chemotherapy, and surgical resection, cancer immunotherapy is another ground-breaking treatment that uses the immune system to destroy and eradicate tumor cells. Numerous cancer immunotherapies have demonstrated encouraging therapeutic results. Cancer immunotherapy still has a lot of issues and difficulties, nevertheless. As evidenced by numerous clinical studies, monoclonal antibodies (MAbs) therapy is a very promising immunotherapy treatment. However, because mAbs are immunogenic, they may result in irreversible adverse events (irAEs), which calls for close observation when used in clinical settings. Higher purity of mAbs requires novel purification techniques, which are time-consuming and expensive to produce. Since patients receiving ICB do not have a high overall immune response rate, accurate and useful biomarkers are required for targeted and customized immunotherapy. mAbs have produced results against advanced-stage malignancies, which previously had dismal prognosis, when combined with chemotherapy.

Furthermore, mixtures including various mAbs also demonstrated a potent anti-tumor impact. In the future, combination therapy might provide mAbs new chances to lessen side effects and enhance therapeutic impact. When cytotoxic drugs are conjugated to monoclonal antibodies (mAbs), precise delivery of payloads to tumors can be facilitated. On the other hand, multispecific antibodies offer new mechanisms that improve specificity and enable transport to previously unreachable compartments. As our knowledge of immunobiology grows and molecular biological techniques advance, the potential applications of monoclonal antibodies (mAbs) therapy are only limited by human creativity. Even though mAb sales are well ahead, small molecule inhibitors for cancer immunotherapy always hold a significant position. Compared to monoclonal antibodies, small molecule inhibitors are easier to control during production and have more developed R&D pipelines, both of which can lower prices. Small molecule inhibitors are helpful for solid tumor

Journal of Science, Management and Technology
ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

immunotherapy due to their good tissue permeability and tunable pharmacokinetic features, which can assist lessen the impact of side effects. There will always be a place for small molecule inhibitors as an efficient mAb substitute and supplement. Proteolysis targeting chimeras, or PROTACs, are a novel kind of small molecule inhibitor: IDO1 PROTACs are being investigated in pre-clinical settings. However, a number of concerns need to be addressed, including those related to safety and potential protein degradation saturation that could restrict the efficacy of the treatment.

Immunotherapy has a number of advantages over targeted therapy and conventional chemoradiotherapy(Odiase, Noah-Vermillion, Simone, & Aridgides, 2021). Significant advancements in the field of tumor immunotherapy have been made possible by the thorough investigation of the anti-tumor immune response mechanism. The increasing use of immunotherapy has made the development of immunological resistance an inevitable issue. Understanding the mechanisms underlying this immunological resistance is still very much in its infancy. We can increase the benefits of immunotherapy for cancer patients' survival by comprehending the mechanisms underlying immune resistance. The combined approach to immunotherapy has a higher therapeutic impact than single-drug therapy(Huang, Chen, Xing, & Zeng, 2021). Clinical trials have demonstrated the significance of immunotherapeutic anticancer medications, such as ACT, ICBs, targeted therapy, chemotherapy, and others, in the combination. The FDA has approved a few combination medications to increase the clinical effectiveness of cancer immunotherapy. More persuasive and efficient combination methods are anticipated as research into the identification of trustworthy biomarkers to inform clinical immuno-oncology decisions continues to progress. An increasing number of TME mechanisms will come to light as tumor immunology, bioinformatics, and sequencing technologies advance. This will advance the field of cancer immunotherapy and open the door to more efficient cancer therapies down the road.

10. Conclusion

Immunotherapies are among the alternative treatments required for HCC. Initial and second line treatment for HCC may greatly benefit from ICIs, according to preliminary clinical trials. Furthermore, novelactive immunotherapies (such cancer vaccines) are being developed and assessed in clinical studies using both individualized mutant neoantigens and new TAAs. Numerous pre-clinical settings and a small number of clinical trials have assessed combination techniques, such as chemotherapy, RFA, or check-point inhibitors combined with vaccinations. It is anticipated that in the upcoming years, HCC would use the latter tactic more often. Immunotherapy holds great promise as a transformative approach for managing chronic inflammatory diseases by targeting dysregulated immune responses and restoring immune homeostasis. While significant progress has been made in developing immunotherapy-induced treatments, further research is needed to overcome existing challenges and optimize treatment outcomes for patients with refractory or debilitating conditions. Continued investment in basic and

ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

translational research, clinical trial design, and regulatory frameworks will be essential to harness the full potential of immunotherapy in revolutionizing the management of chronic inflammatory diseases and improving patients' lives.

Conflict of Interest

There is no conflict of interest regarding this paper. The research work was supported by U&J Digital Consult Limited , an IT and Educational Consulting Firm base in Nigeria .

References

Ahmed, H., Mahmud, A. R., Faijanur-Rob-Siddiquee, M., Shahriar, A., Biswas, P., Shimul, M. E. K., . . . Khan, M. A. (2023). Role of T cells in cancer immunotherapy: Opportunities and challenges. *Cancer Pathogenesis and Therapy, 1*(02), 116-126.

Alard, E., Butnariu, A.-B., Grillo, M., Kirkham, C., Zinovkin, D. A., Newnham, L., . . . Pranjol, M. Z. I. (2020). Advances in anti-cancer immunotherapy: Car-T cell, checkpoint inhibitors, dendritic cell vaccines, and oncolytic viruses, and emerging cellular and molecular targets. *Cancers, 12*(7), 1826.

Bakare, K., Nkeiruka, A., Matthew, U., Ebong, G., & Oyekunle, D. (2024). Immunotherapy Influence On Human Body: Glycan Engineering Antibody-Based Cancer Treatments. *J Comm Med and Pub Health Rep, 5*(03).

Cai, L., Li, Y., Tan, J., Xu, L., & Li, Y. (2023). Targeting LAG-3, TIM-3, and TIGIT for cancer immunotherapy. *Journal of hematology & oncology, 16*(1), 101.

Fountzilas, E., Lampaki, S., Koliou, G.-A., Koumarianou, A., Levva, S., Vagionas, A., . . . Binas, I. (2022). Real-world safety and efficacy data of immunotherapy in patients with cancer and autoimmune disease: the experience of the Hellenic Cooperative Oncology Group. *Cancer Immunology, Immunotherapy, 71*(2), 327-337.

Haanen, J., Ernstoff, M., Wang, Y., Menzies, A., Puzanov, I., Grivas, P., . . . Obeid, M. (2020). Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy. *Annals of Oncology, 31*(6), 724-744.

Harris, D. M., Szymczak, S., Schuchardt, S., Labrenz, J., Tran, F., Welz, L., . . . Oumari, M. (2024). Tryptophan degradation as a systems phenomenon in inflammation–an analysis across 13 chronic inflammatory diseases. *EBioMedicine, 102*.

Hauth, F., Ho, A. Y., Ferrone, S., & Duda, D. G. (2021). Radiotherapy to enhance chimeric antigen receptor T-cell therapeutic efficacy in solid tumors: a narrative review. *JAMA oncology, 7*(7), 1051-1059.

Hou, J., Zhang, H., Sun, B., & Karin, M. (2020). The immunobiology of hepatocellular carcinoma in humans and mice: Basic concepts and therapeutic implications. *Journal of hepatology, 72*(1), 167-182.

Huang, W., Chen, J.-J., Xing, R., & Zeng, Y.-C. (2021). Combination therapy: future directions of immunotherapy in small cell lung cancer. *Translational Oncology, 14*(1), 100889.

Janelle, V., Rulleau, C., Del Testa, S., Carli, C., & Delisle, J.-S. (2020). T-cell immunotherapies targeting histocompatibility and tumor antigens in hematological malignancies. *Frontiers in Immunology, 11*, 507030.

ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

Jhunjhunwala, S., Hammer, C., & Delamarre, L. (2021). Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. *Nature Reviews Cancer, 21*(5), 298-312.

Kamrani, A., Hosseinzadeh, R., Shomali, N., Heris, J. A., Shahabi, P., Mohammadinasab, R., . . . Akbari, M. (2023). New immunotherapeutic approaches for cancer treatment. *Pathology-Research and Practice*, 154632.

Kole, C., Charalampakis, N., Tsakatikas, S., Vailas, M., Moris, D., Gkotsis, E., . . . Schizas, D. (2020). Immunotherapy for hepatocellular carcinoma: a 2021 update. *Cancers, 12*(10), 2859.

Kumari, S., Mukherjee, S., Sinha, D., Abdisalaam, S., Krishnan, S., & Asaithamby, A. (2020). Immunomodulatory effects of radiotherapy. *International Journal of Molecular Sciences, 21*(21), 8151.

Kutija, M. B. (2023). Ophthalmological manifestations of systemic autoimmune diseases *Translational Autoimmunity* (pp. 183-214): Elsevier.

Lee, J., & Kim, E. H. (2023). Mechanisms underlying response and resistance to immune checkpoint blockade in cancer immunotherapy. *Frontiers in Oncology, 13*, 1233376.

Li, R., Hadi, S., & Guttman-Yassky, E. (2019). Current and emerging biologic and small molecule therapies for atopic dermatitis. *Expert Opinion on Biological Therapy, 19*(4), 367-380.

Liang, X., Cheng, H., Liu, C., & Liu, G. (2022). Antigen self-presenting nanovaccine for cancer immunotherapy. *Sci Bull, 67*(16), 1611-1613.

Liu, C., Yang, M., Zhang, D., Chen, M., & Zhu, D. (2022). Clinical cancer immunotherapy: Current progress and prospects. *Frontiers in Immunology, 13*, 961805.

Liu, Z., Xu, K., Jiang, Y., Cai, N., Fan, J., Mao, X., . . . Chen, X. (2021). Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: a modelling study. *International Journal of Epidemiology, 50*(1), 128-142.

Mahajan, R. K., Kokare, D. M., Raut, N. A., & Itankar, P. R. (2022). Phototherapy for skin diseases. *Photophysics and Nanophysics in Therapeutics*, 15-30.

Matthew, U. O., Nwanakwaugwu, A. C., Kazaure, J. S., Nwamouh, U. C., Haruna, K., Okafor, N. U., & Olawoyin, O. O. (2022). Ultra Violet (UV) Light Irradiation Device for Hospital Disinfection: Hospital Acquired Infections Control. *International Journal of Information Communication Technologies and Human Development (IJICTHD), 14*(1), 1-24.

McInnes, I. B., & Gravallese, E. M. (2021). Immune-mediated inflammatory disease therapeutics: past, present and future. *Nature Reviews Immunology, 21*(10), 680-686.

Mukherjee, O., Rakshit, S., Shanmugam, G., & Sarkar, K. (2023). Role of chemotherapeutic drugs in immunomodulation of cancer. *Current Research in Immunology, 4*, 100068.

Nabel, C. S., Severgnini, M., Hung, Y. P., Cunningham-Bussel, A., Gjini, E., Kleinsteuber, K., . . . Felt, K. D. (2019). Anti-PD-1 immunotherapy-induced flare of a known underlying relapsing vasculitis mimicking recurrent cancer. *The Oncologist, 24*(8), 1013-1021.

Najafi, S., & Mortezaee, K. (2023). Advances in dendritic cell vaccination therapy of cancer. *Biomedicine & Pharmacotherapy, 164*, 114954.

Odiase, O., Noah-Vermillion, L., Simone, B. A., & Aridgides, P. D. (2021). The incorporation of immunotherapy and targeted therapy into chemoradiation for cervical cancer: a focused review. *Frontiers in Oncology, 11*, 663749.

ISSN (Print): 1597-7463; eISSN (Online): 2811-2598, Volume 5, Issue 2 https://dx.doi.org/10.4314/hpjsmt.v5i2.12

Parren, P. W., Burton, D. R., Bradbury, A., Huston, J. S., Carter, P. J., Veldman, T., . . . Scott, J. K. (2015). *Antibody Engineering & Therapeutics 2015: The Antibody Society's annual meeting December 7–10, 2015, San Diego, CA.* Paper presented at the Mabs.

Pilones, K. A., Vanpouille-Box, C., & Demaria, S. (2015). *Combination of radiotherapy and immune checkpoint inhibitors.* Paper presented at the Seminars in radiation oncology.

Taylor, J., Gandhi, A., Gray, E., & Zaenker, P. (2023). Checkpoint inhibitor immune-related adverse events: A focused review on autoantibodies and B cells as biomarkers, advancements and future possibilities. *Frontiers in Immunology, 13*, 991433.

Van Damme, H., Dombrecht, B., Kiss, M., Roose, H., Allen, E., Van Overmeire, E., . . . Bardet, P. M. R. (2021). Therapeutic depletion of CCR8+ tumor-infiltrating regulatory T cells elicits antitumor immunity and synergizes with anti-PD-1 therapy. *Journal for immunotherapy of cancer, 9*(2).

Wang, J., Ma, Y., Lin, H., Wang, J., & Cao, B. (2024). Predictive biomarkers for immune-related adverse events in cancer patients treated with immune-checkpoint inhibitors. *BMC immunology, 25*(1), 8.

Warren, C. M., Jiang, J., & Gupta, R. S. (2020). Epidemiology and burden of food allergy. *Current allergy and asthma reports, 20*, 1-9.

Williams, T., Salmanian, G., Burns, M., Maldonado, V., Smith, E., Porter, R. M., . . . Samsonraj, R. M. (2023). Versatility of mesenchymal stem cell-derived extracellular vesicles in tissue repair and regenerative applications. *Biochimie, 207*, 33-48.

Wu, Z., Li, S., & Zhu, X. (2021). The mechanism of stimulating and mobilizing the immune system enhancing the anti-tumor immunity. *Frontiers in Immunology, 12*, 682435.