Clinical Oncology: Case Reports

Mini Review

A SCITECHNOL JOURNAL

Cancer Therapeutics: Next-Generation Immunotherapy

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Abstract

Cancer remains a major global health concern, causing significant morbidity and mortality. The evolving field of cancer research has progressed from early detection to effective treatments aimed at decreasing cancer-related deaths. Molecular biology and genetics advancements have deepened our understanding of cancer biology, leading to breakthroughs in treatment approaches. Immunotherapy has emerged as a promising therapeutic option that uses the patient's immune system to combat cancer. Various immunotherapeutic strategies, including immune checkpoint inhibitors, monoclonal antibodies, mRNA vaccines, and CAR-T cell therapies, offer targeted and efficacious therapies with fewer adverse effects compared to traditional chemotherapy. Combination therapies involving immunotherapy and other modalities have demonstrated improved treatment outcomes, providing new avenues for tailored and more effective cancer treatments. Monoclonal antibodies, especially humanized versions, have revolutionized cancer therapeutics by providing high specificity and lower cytotoxicity. The FDA approvals of immunotherapeutic drugs underscore the progress made. Antibody engineering has further advanced the production of specialized and potent humanized monoclonal antibodies for clinical use. Immune checkpoint inhibitors have shown remarkable results in controlling tumor progression. CAR-T cell therapy and cancer vaccines offer targeted treatments, specifically in hematological cancers. Research on neoantigens and personalized vaccines presents new possibilities for more effective cancer treatments. Collaboration between healthcare organizations and researchers is crucial to drive further advancements and reduce the burden of cancer worldwide. While progress is promising, it is essential to approach these advancements with sensitivity and compassion for patients and caregivers, prioritizing self-care, and support. Continued research and development in the field of immunotherapy and other cutting-edge modalities offer hope for improved cancer care and outcomes globally.

Keywords: Cancer; CAR-T cell therapy; Immunotherapy; Antibody-drug conjugates (ADCs); Monoclonal antibodies (mAbs).

Introduction

Cancer, a complex disease that arises from the uncontrolled proliferation of anomalous cells, continues to affect millions of people worldwide. The disease is characterized by various features, including proliferative signaling, resistance to cell death, and unlimited replication capability, which makes cancer cells more aggressive and promotes invasion and metastasis. Genetic mutations in cancer cells cause them to evade apoptosis and escape cell cycle control mechanisms, leading to an altered and more aggressive phenotype. Several etiologic factors contribute to the development of cancers, including physical, chemical, and biological agents that can cause genetic mutations or DNA damage. Certain infections, lifestyle factors such as tobacco use, alcohol consumption, unhealthy dietary habits, and a sedentary lifestyle can increase the risk of developing cancer.

Despite the advances made in cancer detection and treatment, cancer remains a significant global health problem. According to 2020 estimates from the World Health Organization, cancer accounts for one in six deaths worldwide [1]. Certain types of cancer, including breast, colorectal, lung, and prostate, continue to be more prevalent among men and women. Cancer also poses a significant risk to cancer survivors, as it increases the chances of relapse and recurrence.

As of the year 2023, researchers have made significant progress in understanding the molecular mechanisms behind cancer development and progression. The future of cancer therapy looks promising with the upcoming advancements in new-generation therapeutics, such as CRISPR/Cas9 which is a precise gene editing tool that induces DNA cleavage at targeted sites and instigates the activation of endogenous DNA repair pathways, which can potentially revolutionize cancer treatment [2].

Despite these advancements, significant challenges still arise worldwide due to the increasing number of cancer patients. Therefore, more attention, funding, and implementation of new discoveries are needed to reduce morbidity and mortality rates associated with cancer worldwide.

The purpose of this appraisal is to ascertain the direction of novel cancer treatment modalities, by taking into account ongoing research endeavors and examining the determinants that could potentially shape the development of national and international strategies. Through collaboration and cooperation between healthcare organizations and researchers, we can make significant progress in the fight against cancer and ultimately reduce the burden of cancer worldwide.

Immunotherapy

Immunotherapy is a highly innovative and sophisticated treatment approach that has emerged as a promising therapeutic option for various malignancies, including hematological and solid tumors. This therapy harnesses the patient's own immune system to combat cancer, which has the potential to deliver more

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Received: July 16, 2023; Manuscript No: COCR-23-106482; **Editor Assigned:** July 18, 2023; PreQC Id: COCR-23-106482 (PQ); **Reviewed:** July 24, 2023; QC No: COCR-23-106482 (Q); **Revised:** July 27, 2023; Manuscript No: COCR-23-106482 (R); **Published:** July 29, 2023; DOI: 10.4172/cocr.6(7).302

targeted and efficacious therapies with fewer adverse effects compared to traditional chemotherapy. Currently, available immunotherapeutic strategies include immune checkpoint inhibitors, monoclonal antibodies, mRNA vaccines, and adoptive cell transfer via Chimeric Antigen Receptor T-cell (CAR-T) therapies [3].

The scientific community has recognized the immense potential of immunotherapy, leading to a rapid expansion of research in this area. Recent studies have demonstrated that combining immunotherapy with other therapeutic methods, such as chemotherapy, radiation therapy, and targeted therapy, can result in more effective treatment outcomes. These recent advances in immunotherapeutic methods are paving the way for more promising and tailored treatments for individuals with various malignancies.

The field of cancer immunotherapy has been broadly categorized into passive and active methods that correspond to the immune response elicited. Passive immunotherapy involves the introduction of agents such as lymphocytes, cytokines, or monoclonal antibodies to enhance the existing anti-tumor response. In contrast, active immunotherapy relies on techniques such as vaccination, non-specific immunomodulation, or targeting the immune system using antigen receptors that have been specifically designed to recognize tumor cells. Although immunotherapy has demonstrated promising outcomes, there are various impediments that limit the activation of tumor-specific immune responses, such as CD8+ T-cell dysfunction, and a reduced availability of neoantigens with defects in processing and presentation. Furthermore, immunity resistance can arise from T-cell immune checkpoint pathways. It is, therefore, crucial to examine molecular pathways that limit immunotherapy efficacy and research novel immune checkpoint inhibitors.

Enhancing the response of immunotherapy can be achieved through various strategies such as increasing arrival at tumor sites, augmenting T-cell proliferation, improving continuity, reducing immunosuppression, and preventing T-cell exhaustion.

Monoclonal antibodies (mAbs) are a class of proteins that specifically bind to molecular targets and are produced by B lymphocytes or through synthetic means [1]. They have demonstrated anti-cancer effects in preclinical models and patient studies by targeting appropriate targets. Humanized mAbs have emerged as a highly effective class of cancer therapeutics, with substantial specificity and fewer cytotoxic effects compared to conventional chemotherapeutic agents. mAbs are rapidly developing as immunotherapies, with over 22 FDA-approved immunotherapeutic drugs for oncological diseases. Outstandingly, Olaratumab is a human monoclonal antibody that targets the Platelet-Derived Growth Factor Receptor alpha (PDGFR-α). It represents the first drug of its kind to demonstrate improved overall survival when used in combination with doxorubicin for the treatment of advanced/metastatic Soft Tissue Sarcoma (STS) [4, 5], compared to doxorubicin alone. This breakthrough is a significant milestone in the fight against STS [6].

Studies have shown that mAbs can improve overall survival in cancer patients by activating various anti-cancer mechanisms, such as Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC), promotion of apoptosis, and suppression of cell proliferation. To develop therapeutic mAbs, the hybridoma technology, established in 1975 by Köhler and Milstein [7], uses a fusion of immunized mouse splenocytes capable of producing antibodies with immortal cancer B-cell myeloma cells. While hybridoma technology-based mAbs provide the advantages of low aggregation and high in vivo antigen binding, they have a short half-life, low biological activity, and effector function onset. This statement signifies that muromonab-CD3 was the pioneering therapeutic monoclonal antibody to receive FDA approval in 1985, for use as an anti-rejection medication. However, the field of monoclonal antibody therapeutics has made considerable strides in recent years, with the approval of numerous mAbs to treat various cancers and other illnesses.

The FDA authorized numerous immunotherapeutic drugs for oncological illnesses in 2023, underscoring the significant progress that has been made since the approval of the muromonab-CD3 [1]. Furthermore, advances in antibody engineering and manufacturing techniques have resulted in the creation of highly specialized and potent humanized mAbs that have been employed to manage a diverse range of illnesses outside of oncological disorders.

Antibody engineering has become increasingly popular in producing monoclonal antibodies (mAbs) for clinical use. This entails genetic manipulation, where cloning and sequencing techniques are used to generate various types of mAbs including humanized, fully human, chimeric, and bispecific antibodies [8]. The phage display and transgenic animal technology approaches have produced fully human mAbs utilizing innovative techniques. The constant regions of humanized and human mAbs offer advantages over murine mAbs such as reduced immunogenicity, improved effector functions, and longer serum half-life, making them more efficacious in clinical applications.

Monoclonal antibodies (mAbs) have demonstrated versatility in cancer therapy as they are widely employed as ICIs, ADCs, and bispecific T-cell linkages. They can target pro-tumorigenic compounds and tumor cells thru receptor and ligand blocking, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cellular cytotoxicity mechanisms of action that work together with host immune system components.

The FDA approved chimeric mAb, rituximab, in 1997 as an anti-cancer drug that targets CD20 for treating non-Hodgkin lymphoma [1]. The development of ADCs has resulted in

mAbs coupled with potent cytotoxic agents, leading to the production of new cancer drugs with improved efficacy and fewer side effects.

The use of antibody engineering has become a promising avenue for producing mAbs for clinical applications. Moreover, the development of humanized and human mAbs utilizing modern techniques has shown them to be superior to murine mAbs. mAbs have become vital tools in cancer therapy, displaying diverse clinical applications. Additionally, the development of Antibody-Drug Conjugates (ADCs) has led to the creation of new cancer medications with enhanced therapeutic efficacy and fewer negative effects.

In the year 2023, the world of clinical cancer research is witnessing an exciting expansion in the evaluation of Monoclonal Antibodies (mAbs). This growth suggests that the market share of antibody-drug conjugates (ADCs) could potentially skyrocket, as the development of novel cancer-targeted mAbs and innovative linkers that facilitate controlled drug release is moving ever forward [9].

Moreover, recent studies on T-cell immunobiology have uncovered therapeutic strategies that target immune escape mechanisms in tumors. These strategies result in more effective anti-tumor immune responses, with Immune Checkpoint Inhibition (ICI) emerging as one of the most promising modalities in this regard. Immune checkpoint pathways are responsible for managing T-cell activation, comprising vital molecules such as T-cell surface molecules, T-cell immunoglobulins, and mucin domains, among others.

Interestingly, the overexpression of these molecules can trigger an excessive immune response, making them a crucial target for cytotoxic T-cells to attack and counteract the inhibition of cancer cells. ICI involves the blockade of immune cell receptors or immune checkpoints using mAbs that attach to inhibitory receptors that tumor cells often overexpress, thus enabling T-cells to attack and destroy cancer cells. Prominent targets in antibody development for blocking include PD-1 and CTLA-4, both inhibitory receptors that have proven effective in controlling tumor progression.

In particular, CTLA-4 inhibition transmits an inhibitory signal that blocks both T-cell proliferation and the secretion of cytokine IL-2 for maturation, ultimately leading to tumor progression cessation [1]. Clinical trials of the CTLA-4 inhibitor ipilimumab have yielded highly promising results, with marked increases in survival rates observed among stage III and IV melanoma patients. As a result, the FDA approved ipilimumab in 2011 as the first drug for immune checkpoint blockade, revolutionizing the way we approach cancer treatment and inspiring hope in millions of patients globally.

PD-1, a type of immune checkpoint receptor, functions differently from CTLA-4 in the regulation of T-cell activity. PD-1 promotes T-cell depletion, resulting in the suppression of T-cell response, making it an attractive target for immunotherapy. In 2014, the FDA approved the first PD-1 drug, Nivolumab, for immune checkpoint blockade therapy [10]. Pembrolizumab and cemiplimab are examples of other PD-1 checkpoint inhibitors available. Recently developed immune checkpoint inhibitors, such as atezolizumab and durvalumab, have a different chemical approach but target the PD-1 ligand, PD-L1, and result in the same inhibition of PD-1 activation.

Further studies have explored alternative immune checkpoint inhibitors, which show promise in enhancing immune responses. Lymphocyte Activation Gene-3 (LAG-3) and T-cell immunoglobulin and mucin domain-containing-3 (TIM-3) are examples of immune checkpoints that have been identified as new targets for immune therapy. Other immune checkpoint inhibitors, such as V-domain Ig suppressor of T-cell activation, ITIM domain (TIGIT), and T-cell immunoglobulin may also hold potential as future targets. These discoveries offer exciting new avenues for the development of effective immunotherapies that can harness the body's immune system to fight cancer and other diseases.

In March of 2022, the FDA approved Opdualag (Nivolumab/relatlimab), a fixed-dose combination comprising the programmed death receptor-1 blocking antibody, nivolumab, and the LAG-3 blocking antibody, relatlimab [11]. This therapeutic option is incredibly promising for cancer patients as it presents selectivity in targeting tumor cells while leaving normal cells unharmed.

Chimeric Antigen Receptor-T (CAR-T) cell therapy is one of the most innovative forms of cell-based immunotherapy, genetically engineering T-cells to target tumors. Its popularity in combating hematological cancers is increasing, as it creates antigen-specific CAR-T cells from patients' autologous T-cells in vitro, and later reinfuses them into the patient. Notably, CAR-T cell therapy targets specific cancer antigens, producing potent anti-tumor effects.

Promisingly, nanocarriers loaded with CAR genes and gene editing tools have shown potential in inducing CAR-T cells in vivo, promoting the regression of leukemic cells. Currently, CAR-T-cell therapy has demonstrated excellent preliminary results against B-cell malignancies, primarily targeting blood cancers. The most common antigen targeted for early clinical research in B-cell malignancies is CD19, given its high expression in tumor cells, accessibility through blood and lymphatics, and tolerability of non-tumor effects of B-cell aplasia.

Furthermore, aside from CD19, the FDA has approved BCMA as an antigen target for CAR-T-cell treatment. Early clinical trials show that CAR-T-cell therapy produces improved clinical outcomes against B-cell acute lymphoblastic leukemia. Notably, CAR-T-cell therapy is a rapidly evolving field, and studies continue to explore its potential for other hematological malignancies and solid tumors.

The efficacy of immunotherapy is limited in solid tumors due to tumor histopathological features, the tumor microenvironment's immunosuppressive nature, a lack of tumor-specific antigens, and potential life-threatening toxicities [12]. Despite these challenges, scientists are actively attempting to overcome these barriers, mainly by engineering CAR-T agents. As research on CAR-T therapies expands, promising results will continue to emerge alongside challenges. Thus, CAR-T holds great potential to positively impact cancer treatment. Cancer vaccines, on the other hand, are designed to provoke an immune response against tumor antigens. Though extensive research has been carried out for years, only a few cancer vaccines have been adopted clinically. Cancer vaccine efficacy is dependent on various factors, including the tumor microenvironment, antigen types used, vaccine formulations, and the immune composition of the tumor. Cancer vaccines can be employed either as a preventive measure or therapeutically. Initial cancer vaccines were developed as a preventative measure against viral infections linked to cancer development such as Hepatitis B. Several types of cancer are associated with Human Papillomavirus (HPV) infections.

Human Papillomavirus (HPV) infections have been a public health concern, and three HPV vaccines have been approved for use since 2006 [13]. Health experts recommend individuals over the age of 11 receive the HPV vaccination to prevent HPV-related illnesses. However, preventive vaccines for non-viral cancers have yet to receive approval for human use. This is partly due to the absence of Tumor-Associated Antigens (TAAs) and the risk of cross-reactivity-induced autoimmunity on healthy tissue.

Despite these challenges, therapeutic vaccines for risk-free TAAs are currently undergoing clinical trials without autoimmune side effects being reported. Decades of research have laid the foundation for mRNA vaccines to be utilized as a therapeutic strategy against cancer. mRNA vaccines have demonstrated good tolerability, degradability, and non-infectiousness while producing cell-mediated immunity and humoral responses. Clinical trials have also shown that combining mRNA vaccines with other immunotherapy methods, such as oncolytic viruses, ICIs, and adoptive cell transfer, results in successful tumor regression and relapse prevention.

The field of cancer vaccine development has made significant progress in recent years, but there are still limitations to overcome. One of the challenges is the potential loss of Tumor-Associated Antigens (TAAs) and Major Histocompatibility Complex (MHC) molecules, which are essential for the immune system to recognize and attack tumor cells. Furthermore, immunosuppressive cells in the tumor microenvironment can hinder the effectiveness of cancer vaccines, resulting in an insufficient anti-tumor response. While these limitations have led to cancelations of clinical trials in the past, there is renewed optimism in the field as continued research in new target antigens, adjuvants, and delivery systems is paving the way for more effective cancer vaccine development.

In 2023, there have been several advances in the cancer vaccine research [14]. One approach involves utilizing neoantigens, which are unique antigens present in tumor cells but not present in normal cells. By targeting neoantigens, researchers hope to develop more specific and effective cancer vaccines. Another approach involves the use of personalized cancer vaccines, which are tailored to an individual's unique tumor profile. By using the patient's own tumor cells to create the vaccine, the immune system can be targeted directly to attack the unique characteristics of the tumor.

Success in the future of cancer vaccines depends on transforming "cold" tumors, which lack immune cells, into "hot" tumors, which are infiltrated by immune cells capable of initiating a strong tumor-specific immune response [5, 6, 15, 16]. This approach would allow for the destruction of cancer cells despite the immunosuppressive tumor microenvironment. The development of effective cancer vaccines could provide a new avenue for the treatment and prevention of cancer, and continued research in this field is crucial for progress toward this goal.

Conclusion

In conclusion, cancer remains a significant global health problem, causing one in six deaths worldwide. Despite progress made in cancer detection and treatment, the increasing number of cancer patients continues to pose significant challenges. However, promising advancements in cancer research such as next-generation therapies, particularly immunotherapy, offer hope in the fight against cancer. The recent expansion of research on immunotherapy, including immune checkpoint inhibitors, monoclonal antibodies, mRNA vaccines, CAR-T cell therapy, and cancer vaccines, has the potential to provide more targeted and efficacious therapies with fewer adverse effects compared to traditional chemotherapy. The continued research, exploration, and implementation of these novel treatment approaches have the potential to transform cancer care and improve outcomes for patients worldwide. Through collaboration and cooperation between healthcare organizations and researchers, we can make significant progress in the fight against cancer and ultimately reduce the burden of cancer worldwide.

Immunotherapy has emerged as a highly innovative and sophisticated treatment approach with the potential to revolutionize cancer treatment modalities. Recent studies have shown that combining immunotherapy with other therapeutic methods can result in more effective treatment outcomes. The field of cancer immunotherapy has been broadly categorized into passive and active methods that correspond to the immune response elicited. Additionally, advanced antibody engineering and manufacturing techniques are opening the way for producing highly specialized and potent humanized

monoclonal antibodies that have been employed to manage various illnesses outside of oncological disorders.

The development of immune checkpoint inhibitors, such as CTLA-4 and PD-1/PD-L1 inhibitors, represents a significant milestone in the fight against cancer, inspiring hope in millions of patients worldwide. This innovative approach to cancer treatment is thriving with the approval of numerous immunotherapeutic drugs for oncological diseases. Moreover, CAR-T cell therapy and cancer vaccines have shown remarkable potential in the fight against cancer by harnessing the patient's immune system to combat tumor cells.

Despite the challenges faced by cancer vaccines, including the potential loss of tumor-associated antigens and immunosuppressive cells in the tumor microenvironment, advancements in the field such as the use of neoantigens and personalized cancer vaccines are paving the way for more specific and effective cancer vaccines. Continued research and development in this area offer exciting new avenues to the development of effective immunotherapies and can transform cancer care globally.

Healthcare organizations and researchers' collaboration to explore and implement novel treatment approaches in cancer care offer the potential to transform cancer treatment. As we look to the future, ongoing advancements in cancer research and innovative treatment strategies such as immunotherapy and cancer vaccines hold great promise in the fight against cancer. With the potential to provide more targeted and efficacious therapies with fewer adverse effects compared to traditional chemotherapy, immunotherapy represents a highly innovative and sophisticated treatment approach that has the potential to revolutionize cancer treatment. Additionally, the development of advanced antibody engineering and manufacturing techniques is further opening the way for producing highly specialized and potent humanized monoclonal antibodies that can be used to manage various illnesses outside of oncological disorders. As we make strides in the fields of immunotherapy and cancer vaccines, the future looks optimistic for successful cancer therapies and improved outcomes for patients worldwide. However, challenges persist, and it is important to approach progress with respect and sensitivity toward those currently dealing with this difficult disease. While medical advancements offer hope, patients, and caregivers must also recognize the potential for burnout and prioritize self-care and support. By dedicating ourselves to both scientific progress and compassionate care, we can work towards a future where cancer is no longer a devastating illness.

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