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ADVANCEMENTS IN TARGETED CANCER THERAPIES: FROM MONOCLONAL ANTIBODIES TO IMMUNOTHERAPY

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Abstract

The field of cancer treatment has undergone substantial transformation in recent decades, experiencing notable progress in the development of targeted therapeutic approaches. This abstract provides an overview of the progression from monoclonal antibodies to immunotherapy in the realm of cancer treatment. Monoclonal antibodies initially hailed for their specificity and efficacy in targeting cancer cells, paved the way for the development of more sophisticated immunotherapeutic approaches. Immunotherapy, harnessing body's own immune system to combat cancer, has emerged as a promising avenue for personalized cancer treatment. Key milestones in the development of monoclonal antibodies, including rituximab and Trastuzumab, underscore the transformative impact of targeted therapies on patient outcomes. Furthermore, the advent of immune checkpoint inhibitors, such as Pembrolizumab and Nivolumab, represents a paradigm shift in cancer therapy, offering durable responses and improved survival rates across various malignancies. Despite these advancements, challenges persist, including immune-related adverse events and treatment resistance. Future directions in targeted cancer therapies focus on refining patient selection criteria, elucidating mechanisms of resistance, and exploring novel combination strategies to optimize therapeutic efficacy. In conclusion, the journey from monoclonal antibodies to immunotherapy epitomizes the relentless pursuit of precision medicine in oncology, offering renewed hope for patients battling cancer.

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Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States. In this article, we provide the estimated numbers of new cancer cases and deaths in 2018 in the United States nationally and for each state, as well as a comprehensive overview of cancer occurrence based on the most current population-based data for cancer incidence through 2014 and for mortality through 2015. We also estimate the total number of deaths averted as a result of the continual decline in cancer death rates since the early 1990s and quantify the black-white disparity in cancer mortality by state and age based on the actual number of reported cancer deaths in 2015 [1]. Every year, new cancer cases and cancer deaths are increasing drastically in the United States, causing major economic burdens for patients, healthcare systems, and countries due to healthcare spending, as well as productivity losses from morbidity and premature mortality.

The landscape of cancer therapy has undergone a paradigm shift with the advent of targeted therapies, particularly monoclonal antibodies (mAbs) and immunotherapy [2]. Monoclonal antibodies, designed to target specific antigens expressed on cancer cells, have revolutionized cancer treatment by offering increased specificity and reduced toxicity compared to traditional chemotherapy. The development of hybridoma technology by Köhler and Milstein in the 1970s paved the way for the production of therapeutic mAbs, leading to the approval of rituximab, the first mAb for cancer treatment, in 1997 [3].

Monoclonal antibodies are a type of immunotherapy used in cancer treatment. They work by targeting specific proteins on the surface of cancer cells or in the surrounding environment, which helps the immune system to recognize and destroy cancer cells [4]. Targeting cancer cell, blocking signaling pathways, recruiting immune cells or direct killing cancer cells and modulating the tumor microenvironment are the advanced mechanism are shown in treatment of cancer by Monoclonal antibodies [5-11].

Targeting cancer cells- Monoclonal antibodies are designed to specifically recognize and bind to proteins that are overexpressed or unique to cancer cells. These proteins, known as antigens, may be involved in cell growth, survival, or other processes essential for cancer development and progression.

Blocking signaling pathways- Once bound to the cancer cell surface, monoclonal antibodies can interfere with signaling pathways that promote cancer cell growth and survival. This blockade can inhibit the ability of cancer cells to proliferate and spread.

Recruiting immune cells- Monoclonal antibodies can also act as flags, marking cancer cells for destruction by the immune system. Some monoclonal antibodies are engineered to have a region that binds to immune cells, such as natural killer (NK) cells or macrophages. This binding

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triggers an immune response, leading to the destruction of the tagged cancer cells by the immune cells.

Direct killing- In some cases, monoclonal antibodies are designed to directly induce cell death in cancer cells. This can occur through various mechanisms, such as triggering apoptosis (programmed cell death) or inducing antibody-dependent cell-mediated cytotoxicity (ADCC), where immune cells are recruited to kill the antibody-bound cancer cells.

Modulating the tumor microenvironment - Monoclonal antibodies can also affect the tumor microenvironment, this includes the surrounding blood vessels, connective tissue, and immune cells. By altering the tumor microenvironment, monoclonal antibodies can make it less hospitable to cancer growth and metastasis.

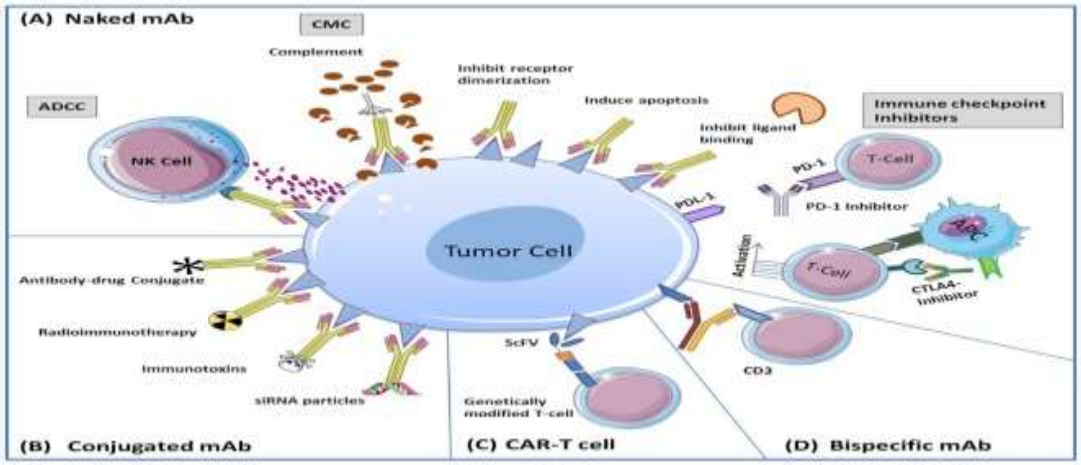

Figure 1. Mechanism of action of mAb therapy. (A) Naked mAb can function through various mechanisms, including antibody dependent cellular cytotoxicity (ADCC) using immune effector cells such as natural killer (NK) cells. Complement-mediated cytotoxicity (CMC) functions through the membrane attack complex and by inhibition of the receptor dimerization, inducing an apoptotic signal or through effecting target cells by blocking the binding of ligand. Immune checkpoint inhibitors, including PD-1, function by blocking the T-cell-inhibitory receptors and CTLA-4, which function through activation of T-cell function. (B) Conjugated mAb includes payload antibody for delivery of specific drugs or chemotherapy agents directly to the tumor cells, radioimmunoconjugates to deliver radioisotopes to the cancer cells, immunotoxins to deliver highly toxic drugs to the target cells, and siRNA particles to downregulate a target gene. (C) CAR T-cell therapy uses a genetically engineered T cell to target a specific antigen on tumor cells. (D) Bispecific mAbs consist of two arms, with one arm recognizing cancer cells and the other activating antigens on immune effector cells including CD3 [12] .

Thus due to these mode of actions monoclonal antibodies offer a targeted approach to cancer treatment, with the potential for fewer side effects compared to traditional chemotherapy and radiation therapy. They can be used alone or in combination with other cancer treatments, such as chemotherapy, radiation therapy, or other immunotherapies, to enhance their effectiveness.

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The field of targeted cancer therapy has witnessed remarkable advancements, including the development of monoclonal antibodies targeting various signaling pathways crucial for cancer cell proliferation and survival. Examples include Trastuzumab targeting HER2 in breast cancer and bevacizumab targeting VEGF in colorectal, lung, and renal cancers [13-14]. These mAbs have demonstrated significant clinical efficacy and have become integral components of standard cancer treatment regimens [15].

Table 1: List of some monoclonal antibodies used as anticancer agents along with their targets [16]

Monoclonal Antibody	**Anticancer Target**
Trastuzumab	HER2/neu (human epidermal growth factor receptor 2)
Rituximab	CD20 (cluster of differentiation 20)
Pembrolizumab	PD-1 (programmed cell death protein 1)
Ipilimumab	CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)
Bevacizumab	VEGF (vascular endothelial growth factor)
Cetuximab	EGFR (epidermal growth factor receptor)
Daratumumab	CD38 (cluster of differentiation 38)
Nivolumab	PD-1 (programmed cell death protein 1)
Atezolizumab	PD-L1 (programmed death-ligand 1)
Brentuximab vedotin	CD30 (cluster of differentiation 30)

In recent years, immunotherapy has emerged as a groundbreaking approach in cancer treatment, harnessing the power of the immune system to recognize and eliminate cancer cells. Checkpoint inhibitors, such as Pembrolizumab and Nivolumab, have shown remarkable success in various malignancies by blocking immune checkpoints like PD-1 and CTLA-4, thereby restoring antitumor immune responses. Additionally, adoptive cell therapies, such as chimeric antigen receptor (CAR) T-cell therapy, have shown unprecedented efficacy in hematologic malignancies, offering durable remissions in patients with relapsed or refractory disease [17-23].

The synergistic combination of monoclonal antibodies and immunotherapy has further expanded the treatment armamentarium against cancer shown in table 2. Immune checkpoint inhibitors have been successfully combined with targeted agents to enhance antitumor immune responses, leading to improved outcomes in patients across various cancer types. Moreover, bispecific antibodies and antibody-drug conjugates (ADCs) represent innovative strategies to simultaneously target cancer cells and engage the immune system for enhanced therapeutic efficacy [24].

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Table 2: List of few synergistic combinations of monoclonal antibodies used as anticancer agents [25-35]

Combination Therapy	Monoclonal Antibodies with anticancer drugs
Rituximab plus Bendamustine	Rituximab (anti-CD20) Bendamustine (alkylating agent)
Trastuzumab plus Pertuzumab	Trastuzumab (anti-HER2) Pertuzumab (anti-HER2)
Pembrolizumab plus	Pembrolizumab (anti-PD-1)
Ipilimumab	Ipilimumab (anti-CTLA-4)
Atezolizumab plus Bevacizumab	Atezolizumab (anti-PD-L1) Bevacizumab (anti-VEGF)
Nivolumab plus Ipilimumab	Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4)
Cetuximab plus FOLFOX	Cetuximab (anti-EGFR) FOLFOX (combination chemotherapy: Oxaliplatin, 5-Fluorouracil, Leucovorin)
Daratumumab plus	Daratumumab (anti-CD38)
Bortezomib plus Dexamethasone	Bortezomib (proteasome inhibitor) Dexamethasone (steroid)
Brentuximab vedotin plus CHP (cyclophosphamide, doxorubicin, prednisone)	Brentuximab vedotin (anti-CD30 linked to a microtubule inhibitor) Cyclophosphamide (alkylating agent) Doxorubicin (anthracycline) Prednisone (steroid)

Challenges and Future Prospective

Despite these remarkable advancements, challenges remain in the field of targeted cancer therapies. Resistance mechanisms, off-target effects, and immune-related adverse events pose significant clinical hurdles that necessitate ongoing research efforts. Additionally, the high cost of targeted therapies limits their accessibility to patients, highlighting the need for affordable treatment options and healthcare policies to ensure equitable access. Cancer cells can develop resistance to monoclonal antibodies over time, rendering the treatment less effective. This resistance can occur through various mechanisms, including mutations in the target antigen, activation of alternative signaling pathways, or downregulation of antigen expression [36-37]. Monoclonal antibodies may not be effective in all types of cancer or in all patients within a specific cancer type. Some cancers may lack appropriate target antigens, or the tumor microenvironment may hinder antibody binding and immune response. While monoclonal antibodies are generally well-tolerated, they can still cause side effects, including infusion

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reactions, immune-related adverse events (such as autoimmune disorders), and off-target effects on healthy tissues expressing the target antigen [38-40]. Monoclonal antibodies derived from non-human sources (such as murine antibodies) may provoke immune responses in patients, leading to the formation of anti-drug antibodies. This can reduce the efficacy of treatment and increase the risk of allergic reactions. Monoclonal antibody therapies are often expensive, limiting access for some patients, especially in healthcare systems with limited resources or in regions with socioeconomic disparities. Monoclonal antibodies are typically administered intravenously in clinical settings, requiring frequent hospital visits for patients. This can be burdensome for patients and healthcare providers and may affect treatment adherence. While combination therapies involving monoclonal antibodies can enhance treatment efficacy, they also introduce challenges related to dose optimization, scheduling, and management of potential drug interactions and overlapping toxicities. Identifying predictive biomarkers to select patients who are most likely to benefit from monoclonal antibody therapy remains a challenge. Biomarker-driven patient stratification is crucial for optimizing treatment outcomes and minimizing unnecessary exposure to potential side effects. These challenges require ongoing research and development efforts aimed at improving the efficacy, safety, and accessibility of monoclonal antibody-based immunotherapies in cancer treatment [41-42].

The future of cancer treatment lies in personalized medicine, wherein therapies are tailored to individual patients based on their genetic makeup, tumor characteristics, and immune profile. Advancements in genomic sequencing technologies, coupled with computational algorithms, will enable oncologists to identify specific mutations driving cancer growth and select targeted therapies with higher efficacy and fewer side effects. Continued research into the molecular mechanisms underlying cancer will unveil novel targets for therapy. Emerging techniques such as proteomics, metabolomics, and single-cell sequencing will enhance our understanding of tumor biology, facilitating the development of highly specific inhibitors and immunotherapies that selectively target cancer cells while sparing normal tissues. Combination therapies that harness the immune system's power alongside conventional treatments like chemotherapy, radiation, or targeted therapy will become increasingly prevalent. By leveraging synergistic interactions between different modalities, such as checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and cytokine-based therapies, clinicians can enhance treatment responses and overcome resistance mechanisms [43]. Resistance to targeted therapies remains a significant challenge in cancer treatment. Future strategies will focus on elucidating the diverse mechanisms of resistance, including genetic mutations, tumor heterogeneity, and immune evasion, and developing innovative approaches to circumvent or overcome them. This may involve the use of adaptive therapies that dynamically adjust treatment regimens based on real-time monitoring of tumor evolution and response. Advances in nanotechnology hold immense promise for improving drug delivery and enhancing the efficacy of targeted cancer therapies. Nanoparticle-based delivery systems can improve drug solubility, bioavailability, and tumor penetration while minimizing off-target effects. Moreover, functionalized nanoparticles can be

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engineered to selectively deliver therapeutic agents to cancer cells, further enhancing treatment specificity. Liquid biopsies, which involve the analysis of circulating tumor cells, cell-free DNA, and other biomarkers in peripheral blood, offer a non-invasive means of detecting cancer and monitoring treatment response. As technologies for detecting and analyzing these biomarkers continue to evolve, liquid biopsies will play an increasingly important role in early cancer detection, treatment selection, and disease monitoring [44-45]. Artificial intelligence (AI) and machine learning algorithms are poised to revolutionize cancer care by analyzing vast amounts of clinical and molecular data to identify patterns, predict treatment outcomes, and optimize therapeutic strategies. AI-driven approaches can assist clinicians in interpreting complex datasets, guiding treatment decisions, and identifying personalized treatment regimens tailored to each patient's unique profile.

Conclusion

The journey from monoclonal antibodies to immunotherapy represents a remarkable evolution in the field of targeted cancer therapies. Monoclonal antibodies have paved the way by providing effective and specific targeting of cancer cells, leading to improved outcomes for patients across various malignancies. However, the advent of immunotherapy, particularly immune checkpoint inhibitors and CAR T-cell therapy, has heralded a new era of precision medicine, offering unprecedented efficacy and durable responses in subsets of patients. As we look to the future, the convergence of monoclonal antibodies and immunotherapy, along with advances in precision medicine and our understanding of cancer biology, holds great promise for further enhancing therapeutic outcomes and addressing the challenges of treatment resistance and tumor heterogeneity. By embracing innovation, collaboration, and a patient-centered approach, we can continue to push the boundaries of science and bring hope to individuals affected by cancer. With ongoing research and clinical trials, we are poised to unlock new frontiers in targeted cancer therapy, ultimately transforming the landscape of cancer treatment and improving the lives of patients worldwide.

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