Immunotherapy for Resistant Cancers: Review of Present and Future Directions

Abstract

Cancer resistance to conventional therapies remains a significant challenge in oncology, leading to treatment failure and poor patient outcomes. Immunotherapy has emerged as a promising approach to overcome resistance by harnessing the body's immune system to recognize and eliminate cancer cells. This review discusses the mechanisms of resistance in cancer, the advances in immunotherapy strategies, and how these therapies are overcoming resistance in various cancer types. It also highlights the clinical outcomes of recent trials and explores future directions in the field.

Keywords: Immunotherapy, Resistant cancers, Immune checkpoint inhibitors, CAR T-cell therapy, Tumor microenvironment, Combination therapy, Biomarkers.

1. Introduction

Cancer remains one of the leading causes of death worldwide, with resistance to conventional therapies posing a significant barrier to successful treatment (Siegel et al., 2020). Traditional treatments like chemotherapy and radiation therapy often face challenges due to the cancer cells' ability to develop resistance mechanisms, leading to relapse and metastasis (Holohan et al., 2013).

1.1. Immune surveillance and immunoediting

The complex relationship between cancer and the host immune system has been a subject of study for decades. The idea of cancer immunosurveillance was first introduced in 1909 by Ehrlich, who proposed that the host immune system continuously identifies and eliminates emerging tumors before they become clinically detectable (Ehrlich, 1909). This concept was further refined in 1970 by Burnet, who suggested that genetic mutations leading to malignancy frequently occur in somatic cells, with the immune system playing a vital role in eliminating or suppressing these potentially harmful mutant cells (Burnet, 1970) (Muenst et al., 2016). Experimental evidence has since validated this theory, particularly through studies showing a higher incidence of malignant tumors in immunodeficient mice and humans (Dunn et., 2004), (Mapara and Sykes, 2004). Furthermore, individuals receiving immunosuppressive therapy following organ transplantation, as well as HIV-positive patients, exhibit a significantly increased risk of developing malignancies (Mapara and Sykes, 2004). But the occurrence of malignant tumors in individuals with fully functional immune systems indicates that immunosurveillance is only one aspect of the process (Muenst et al., 2016). Over the past two decades, this concept has been expanded and refined into the theory of "immunoediting" (Mittal et., 2014). Immunoediting is now widely recognized as a dynamic process that not only prevents tumor formation but also influences the immunogenic profile of developing tumors. This process is characterized by three interrelated stages: elimination, equilibrium, and escape (Mittal et., 2014). These stages are not discrete phases but rather a continuum of interactions between the tumor and the immune system. The balance between these stages shifts based on the condition of the immune system and the intrinsic or acquired

characteristics of the tumor cells (Muenst et al., 2016). Elimination refers to the process by which developing tumors are effectively destroyed by the innate and adaptive immune systems through various mechanisms (Mittal et., 2014) (Muenst et al., 2016). When the immune system completely eradicates the tumor, elimination marks the final stage of immunoediting. However, if some tumor cells evade destruction, they may enter a state of equilibrium where the immune system suppresses tumor growth, and the cells remain dormant for extended periods. The longest of the three stages, "equilibrium," can last up to 20 years between the first changing event and the clinical identification of the tumour (Mavi et al., 2023). Eventually, tumor cells may escape immune control, allowing them to proliferate unchecked and form clinically detectable tumors. This escape is facilitated by mechanisms such as reduced immune recognition, increased resistance to immune cell attacks, or the establishment of an immunosuppressive tumor microenvironment. Emerging evidence suggests that tumors can actively create an immunosuppressive environment and recruit specific immune cells that promote tumor growth and progression (Galdiero et., 2013) (Joyce and Fearon, 2015) (Muenst et al., 2016).

Recent advancements in understanding the human immune system and the mechanisms by which tumors evade immune surveillance have paved the way for innovative therapeutic strategies. These approaches are now regarded as some of the most significant medical breakthroughs in recent years (Muenst et al., 2016). Immunotherapy has revolutionized cancer treatment by leveraging the body's immune system to fight cancer cells (Pardoll, 2012). Unlike traditional therapies, immunotherapy can provide durable responses and has shown efficacy in resistant cancers (Sharma & Allison, 2015).

1.2. Objectives

This review explores the mechanisms behind cancer resistance and the advances in immunotherapy that are helping to overcome these challenges.

2. Mechanisms of Resistance in Cancer

Understanding the mechanisms of resistance is crucial for developing effective therapies.

2.1. Genetic Mutations

Cancer cells can acquire mutations that alter drug targets, rendering therapies ineffective (Vasan et al., 2019). These mutations can lead to overexpression of drug efflux pumps, changes in cell cycle regulators, and activation of alternative survival pathways (Holohan et al., 2013).

2.2. Tumor Microenvironment

The tumor microenvironment (TME) consists of various cells, cytokines, and extracellular matrix components that support tumor growth and contribute to resistance (Hinshaw & Shevde, 2019). Hypoxia within the TME can induce angiogenesis and promote a more aggressive phenotype (Vaupel & Multhoff, 2018).

2.3. Immune Evasion

Cancer cells can evade immune detection through several mechanisms, such as downregulating antigen presentation, secreting immunosuppressive cytokines, and expressing immune checkpoint molecules (Beatty & Gladney, 2015). These strategies inhibit immune cell activation and allow cancer cells to proliferate unchecked.

3. Advances in Immunotherapy

Recent advancements have led to various immunotherapy strategies that can overcome resistance.

3.1. Immune Checkpoint Inhibitors

Immunotherapy, including approaches like adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs), is a form of cancer treatment that leverages the immune system to target and destroy tumor cells (Sadeghi et al., 2021). Used either as a standalone therapy or in combination with conventional treatments such as radiotherapy and chemotherapy, immunotherapy has achieved significant success and is now a standard treatment option for various types of cancer (Barbari et al., 2020). Immune checkpoints are regulatory pathways that maintain self-tolerance. Cancer cells exploit these checkpoints to avoid immune destruction (Pardoll, 2012). But only a subset (20–40%) of patients benefit from this therapy, highlighting the growing need to develop predictive biomarkers (Shiravand et al., 2023).

3.1.1. PD-1/PD-L1 Inhibitors

Humanized monoclonal antibodies targeting immune checkpoint proteins have been successfully utilized in treating patients with metastatic melanoma, renal cell carcinoma, head and neck cancers, and non-small cell lung cancer. Programmed cell death protein 1 (PD-1) and its ligand PD-L1 are critical in downregulating immune responses. The US FDA has approved three categories of immune checkpoint inhibitors (ICIs), including PD-1 inhibitors (nivolumab, pembrolizumab, and cemiplimab) and PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab) (Shiravand et al., 2023). Inhibitors like nivolumab and pembrolizumab block this interaction, restoring T-cell activity against tumors (Topalian et al., 2015).

3.1.2. CTLA-4 Inhibitors

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another checkpoint that negatively regulates T-cell activation. CTLA-4, a protein belonging to the immunoglobulin superfamily, was initially identified in a cytotoxic T lymphocyte cDNA library and is predominantly expressed by activated T cells. Exclusively expressed on T cells, CTLA-4 plays a crucial role in regulating the extent of T cell activation during the early stages of the immune response. Its primary function is to inhibit the activity of CD28, a co-stimulatory receptor essential for T cell activation (Shiravand et al., 2023). The US FDA approved, Ipilimumab, a CTLA-4 inhibitor, enhances immune responses and has shown efficacy in melanoma (Hodi et al., 2010).

3.2. CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy involves genetically engineering T-cells to express receptors that recognize specific tumor antigens (June et al., 2018). Chimeric Antigen

Receptors (CARs) are genetically engineered receptor proteins designed to enable T lymphocytes to recognize and target specific proteins on tumor cells. The antigen-recognition domains of these modified receptors are derived from monoclonal antibodies (mAbs). As a result, CAR structures provide T cells with the exceptional specificity, high affinity, and diversity of mAbs against tumor antigens, while also retaining their inherent cytolytic activity, enhancing their effectiveness against cancer cells (Mavi et al., 2023). CAR T-cell therapy has shown remarkable success in hematological malignancies resistant to conventional therapies (Maude et al., 2018). Although CAR-T cell therapy has achieved significant clinical responses in specific subgroups of B cell leukaemia or lymphoma, various difficulties restrict CAR-T cell therapy's therapeutic effectiveness in solid tumours and haematological malignancies. Severe life-threatening toxicities, poor anti-tumour effectiveness, antigen escape, restricted trafficking, and limited tumour penetration are all barriers to successful CAR-T cell treatment. Furthermore, CAR-T cell interactions with the host and tumour microenvironment have a significant impact on their activity. Furthermore, developing and implementing these therapies necessitates a complicated staff. Innovative methodologies and tactics to engineering more potent CAR-T cells with greater anti-tumour activity and less toxicity are required to address these important difficulties (Mavi et al., 2023).

3.3. Cancer Vaccines

In recent years, tumor microenvironment-associated cancer vaccine therapies have garnered significant attention. These innovative approaches aim to harness and amplify the body’s natural immune response by targeting specific antigens found within the tumor microenvironment. The ultimate objective is to achieve a complete clinical response, characterized by the elimination or significant reduction of measurable cancer cells (Kaczmarek et al., 2023). With the potential to transform cancer treatment, these therapies are a promising area of exploration for both researchers and clinicians. However, despite over a century of research, the efficacy of therapeutic cancer vaccines has been inconsistent, particularly in patients with advanced cancers. Challenges include the heterogeneity of the tumor microenvironment, the presence of immunosuppressive cells, and the ability of tumors to evade immune responses through escape mechanisms. Overcoming these limitations remains critical to realizing the full potential of cancer vaccine therapies (Kaczmarek et al., 2023) (Schlom, 2012). Sipuleucel-T, approved for metastatic prostate cancer, is an example of an autologous cellular immunotherapy (Kantoff et al., 2010) (Kaczmarek et al., 2023).

3.4. Oncolytic Viruses

Oncolytic viruses (OVs) represent a promising new class of cancer therapeutics with several unique advantages. These include selective replication within tumor cells, the ability to deliver multiple eukaryotic transgene payloads, the induction of immunogenic cell death, the promotion of antitumor immunity, and a favorable safety profile with minimal overlap in toxicity with other cancer therapies. To date, four OVs and one non-oncolytic virus have been approved for cancer treatment worldwide, though talimogene laherparepvec (T-VEC) remains the only widely approved oncolytic virus therapy. T-VEC, initially approved in 2015, is indicated for the treatment of patients with recurrent melanoma following initial surgery (Shalhout et al., 2023) (Andtbacka et al., 2015). Despite growing research interest, a deeper understanding of the biology and pharmacology of OVs is essential to fully unlock

their therapeutic potential in cancer patients. Addressing these knowledge gaps will be crucial for optimizing the clinical utility of OVs and expanding their application across different cancer types.

3.5. Adoptive Cell Transfer

Adoptive cell therapy (ACT) is an emerging and rapidly advancing cancer treatment strategy that has demonstrated significant potential in managing various types of cancer. The approach involves isolating and activating a patient's immune cells ex vivo and reintroducing them into the body to specifically recognize and destroy cancer cells (Du et al., 2023). Currently, the most commonly used forms of ACT include tumor-infiltrating lymphocytes (TILs), genetically engineered immune cells and dendritic cell (DC) vaccines. Advances in cell culture techniques and genetic engineering have expanded the clinical applications of ACT, particularly in the treatment of hematologic malignancies. Furthermore, numerous ACT-based regimens are undergoing clinical trials, highlighting their potential to transform cancer treatment and improve patient outcomes. (Du et al., 2023) (Rosenberg & Restifo, 2015).

4. Overcoming Resistance with Immunotherapy

Immunotherapy can overcome resistance through various strategies.

4.1. Combination Therapies

Combining immunotherapy with other treatments can enhance efficacy and overcome resistance mechanisms.

4.1.1. Immunotherapy with Chemotherapy

Chemotherapy can modulate the immune system by increasing antigen presentation and reducing immunosuppressive cells. Checkpoint inhibitors are increasingly being incorporated into standard chemotherapy regimens in numerous clinical trials. Notable success has been observed in non-small cell and small cell lung cancers, urothelial carcinoma, head and neck cancers, as well as gastric and esophageal cancers. Additionally, promising outcomes have been reported in triple-negative breast cancer and pancreatic cancer, highlighting the potential of this combined approach (Salas-Benito et al., 2021) (Gandhi et al., 2018).

4.1.2. Immunotherapy with Targeted Therapy

The causes of primary and secondary resistance to immunotherapy are multifaceted, stemming not only from tumor-intrinsic factors but also from the intricate interactions between cancer cells and their surrounding microenvironment (Murciano-Goroff et al., 2020). Targeted therapies can alter the TME and increase tumor immunogenicity. Melanoma was one of the first tumor types to benefit from this new care frontier by introducing specific inhibitors for v-Raf murine sarcoma viral oncogene homolog B (BRAF), mitogen-activated protein kinase kinase (MEK), v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), and, recently, immunotherapy (Falcone et al., 2020) (Eroglu et al., 2018).

4.1.3. Immunotherapy with Radiation Therapy

Radiotherapy, the most commonly used oncological treatment, has attracted considerable attention as a combination partner for immunotherapy owing to its well-known and predictable safety profile, widespread clinical availability, and potential for immunostimulatory effects (Galluzzi et al., 2023). Combining radiation with immunotherapy has led to the "abscopal effect," where untreated tumors shrink following localized radiation (Demaria et al., 2005). Numerous clinical studies are exploring the combination of radiotherapy and immune checkpoint inhibitors (ICIs) for managing advanced or metastatic solid cancers, driven by preclinical evidence suggesting a synergistic interaction between these treatments. However, the optimal strategies for integrating these modalities into cancer therapy remain uncertain (Rajeev-Kumar and Pitroda, 2023).

4.2. Biomarkers for Predicting Response

Identifying biomarkers can help predict which patients will benefit from immunotherapy. Several predictive molecular biomarkers, including PD-L1 expression and high tumor mutation burden, have shown utility in discovering lung cancer patient groups that would benefit from ICIs. PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) are among the markers being studied (Goodman et al., 2017). a new field of research opened to discover imaging biomarkers in addition to predictive molecular biomarkers. PET and single-photon emission computed tomography (SPECT) imaging utilize radioisotopes to label specific cells to target and visualize through imaging. Many clinical trials are currently underway to examine various imaging markers or radiolabels that could provide prognostic insight of response to anti-PD-1/PD-L1 antibodies (Pharaon et al., 2020).

5. Clinical Trials and Outcomes

5.1. Success Stories

- **Melanoma:** Immune checkpoint inhibitors have transformed melanoma treatment, improving survival rates (Robert et al., 2015).
- **Lung Cancer:** Pembrolizumab has shown efficacy in NSCLC with high PD-L1 expression (Reck et al., 2016).
- **Lymphoma:** CAR T-cell therapy has achieved high response rates in refractory diffuse large B-cell lymphoma (Neelapu et al., 2017).

5.2. Challenges and Limitations

- **Immune-Related Adverse Events:** Autoimmune toxicities can limit therapy use (Postow et al., 2018).
- **Resistance to Immunotherapy:** Some tumors develop resistance through alternative pathways (Sharma et al., 2017).

- **Cost and Accessibility:** High costs of cancer drugs can limit patient access to these therapies. The median cost of cancer treatment in the United States (USA) and Europe at the time of approval by the Food and Drug Administration (FDA) or the European Medicines Agency has escalated significantly, rising from less than $100 per month in the 1990s to approximately $10,000 per month by 2011. Global cancer drug sales are projected to increase even further in the next few years, from $193 billion USD in 2022 to $377 billion USD by 2027 (Weth et al., 2024)

6. Future Directions

6.1. Novel Targets and Therapies

Research is ongoing to identify new immune checkpoints and develop novel inhibitors (Chen & Flies, 2013). Targeting co-stimulatory molecules like OX40 and 4-1BB is under investigation (Weinberg et al., 2011).

6.2. Personalized Medicine

Integrating genomic data can help tailor immunotherapies to individual patients (Havel et al., 2019). Personalized neoantigen vaccines are being explored to enhance immune responses (Ott et al., 2017).

6.3. Role of the Microbiome

The gut microbiome influences immune responses and may impact immunotherapy efficacy (Gopalakrishnan et al., 2018). Modulating the microbiome could enhance treatment outcomes.

7. Conclusion

Immunotherapy has significantly advanced the treatment of resistant cancers, offering hope for patients who previously had limited options. By understanding resistance mechanisms and leveraging the immune system, therapies can be developed to overcome these challenges. Continued research and clinical trials will further refine these strategies, leading to improved patient outcomes.

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