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Research Article

IMMUNOLOGICAL COMPOUNDS FOR CANCER THERAPY

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Abstract

In recent years, cancer therapy has envolved from traditional methods such as surgery, radiotherapy, chemotherapy, targeted therapies, including immuno-oncology (IO) This innovative approach uses the body the immune system's role in fighting cancer cells has shown exceptional success. Biomarker testing, particularly PD-L1, is now mandatory before treatments such as pembrolizumab (Keytruda) for lung, stomach, head and neck cancer, and atezolizumab (Tecentriq) for cervical and endometrial cancer cancer but PD-L1 is important for other cancers is uncertain and Despite progress, challenges in managing the side effects and high costs of IO persist, causing concern for the NHS and other healthcare systems. Furthermore, the IO pipeline includes promising CAR-T cell therapies and cancer therapies, although these present unique toxicity and cost challenges. Immunotherapies can be used as a delivery mechanism by attaching a monoclonal antibody to a chemotherapy drug to make an antibody drug conjugate (ADC). The antibody seeks out and hones in on a specific molecule on the tumor cell, bringing the chemotherapy with it.

Keywords: Immune Checkpoint Inhibitors, Immune-oncology, Immunotherapies

1. Introduction

Increase in cancer incidence accompanied by asignificant decline in mortality. This trend reflects advances in early detection and treatment of cancers including more than 200 different types[1].

Cancer treatments began to evolve in the 1800s, made possible by the development of general anesthetics. Surgery offered unprecedented methods of eradication, especially when tumors were small and well defined. This was followed by radiotherapy in the late 19th century, rays to damage tumor cell DNA, interfere with vital biological processes and induce cell death[2].

The advent of chemotherapy in the 1940s, inspired by the discovery of myelosuppression in individuals exposed to mustard gas during World War II, led to speculation that leukemia and other proliferative diseases might be respond to drugs that can target highly proliferating cells. The introduction of chemotherapy marked a pivotal era, expanding treatment options to manage solid or metastatic cancers that could not be adequately managed with surgery or radiotherapy alone Period went on to develop chemotherapeutic agents to target different phases of the cell cycle, often used in combination to reduce the development of resistance[3].

A fourth major breakthrough in cancer therapy came with targeted therapies,a small molecule kinase inhibitor, delivered its focused primarily on the mutated BCR-ABL protein found in tumor cells of chronic myeloid leukemia (CML) patients. This approach is called therapy, and it uses modern systems biology and drug discovery techniques to develop therapies tailored to unique biomarkers that bind to tumor cells while keeping healthy cells out.

Currently, a combination of therapy is widely used to ensure complete eradication of cancer cells Notably, immuno-oncology (IO) therapies has emerged as a promising strategy over the past decade. IO therapies, including checkpoint inhibitors, use the immune system to target and eliminate tumor cells. Important immune regulatory proteins are used by tumors to avoid detection and destruction by the immune system. IO treatments disrupt these pathways, freeing the immune system to better recognize and attack cancer cells[4].

2. History

The history of immuno-oncology (IO) begins with the discovery of spontaneous activity in cancer patients. One of the pioneers who explored the idea of IO was William Cole in the 1890s. Cole said cancer patients who developed the infection after surgery showed faster improvement compared to those who did not. This discovery led him to investigate the use of bacteria to stimulate the body's natural anti-cancer response. Kole developed what came to be known as Kole toxin, derived from damaged bacteria, considered one of the first treatments for IO[5].

Another milestone in the development of IO was the use of the vaccine, originally developed for tuberculosis (TB) in the 1900's in a study of tuberculosis patients who received BCG showed a lower incidence of cancer. In addition to studies showing that individuals immunized with BCG at birth newly, leukemia decreased later in life[6].

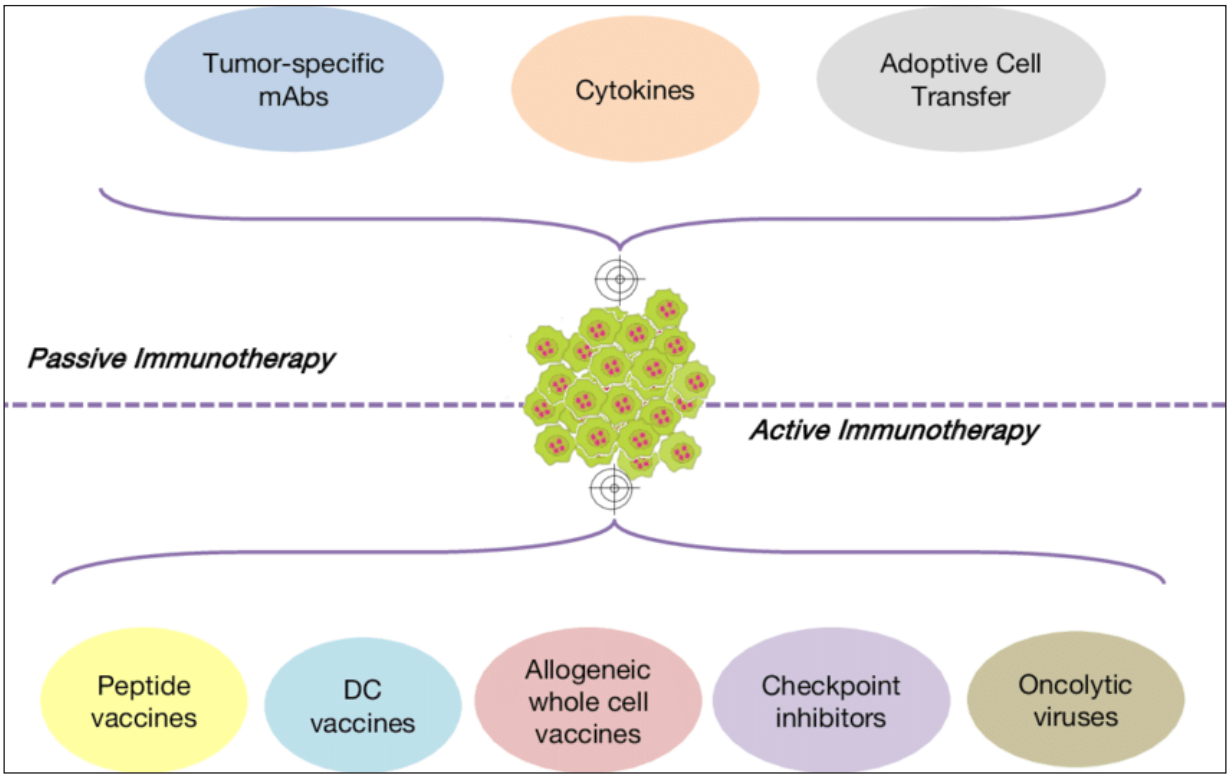

Figure 1: Cancer immunotherapy approaches are classified into passive and active. Passive immunotherapy includes the use of tumorspecific mAbs, cytokines and adoptive cell transfer, whereas active immunotherapy refers to peptide, DC or allogeneic whole cell vaccines, checkpoint inhibitors and oncolytic viruses. DC, dendritic cell

These early discoveries and experiments laid the foundation for the study of immunology and cancer, demonstrating the ability to harness the immune system to fight cancer and research and subsequent developments developed various immunotherapies, including vaccines and adoptive cell therapy.

3. Categorizationof (IO) Agents

The categorization of immuno-oncology (IO) agents presents challenges due to significant overlap and ambiguity, particularly with emerging therapies.[14] Various classification systems have been proposed, including those based on treatment type, cancer type, or mechanistic perspective[7].

This study uses a classification system using tables. However, the classification of IO agents has been found to be not straightforward. For example, immune checkpoint inhibitors (ICPis) ICPis itself is a type of mAb, although Organizations such as the Cancer Research Institute the IO drugs can be classified according to treatment type or cancer type etc. you can use wider categories. Another classification method is based on a technical approach, where IO operators are divided into either "active" or "passive" classes. However, this separation may oversimplify the complexity of drug and patient-tumor interactions. In this review, inactive mAbs, including ICPis, and those targeted to external and cellular targets are grouped, whereas combined mAbs (such as antibody-drug conjugates, immunotoxins) are grouped and in active therapy separately[8].

Among inactive IO drugs, mAbs represent the largest and best defined group. The subclass of mAbs, ICPis, has been highlighted as particularly promising in current research. Active antibodies, classified separately, CAR-T cells primary care is gaining increasing interest as an emerging treatment [18]. In this way, T cells collected from cancer patients can be modified ex vivo and re-administered to the same patient. While only two CAR-T cell therapies are currently approved (Yescarta by Kite Pharma and Kymriah by Novartis), there are many others in development[9].

In the field of immuno-oncology (IO), drug discovery and development are rapidly advancing towards a pharmacogenomic approach. This approach involves identifying biomarkers in tumor biopsy material to predict the most efficacious therapies for individual patients. For major IO drug families such as anti-PD-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) drugs, the relationship between target expression and treatment response.Despite the importance of PD-L1 expression as a biomarker, there are reports of treatment response regardless of PD-L1 expression levels. Furthermore, there is uncertainty about the thresholds for defining 'positive' and 'negative' biomarker expression values, particularly for PD-L1. Current definitions, such as 'weak positive' (1-49% expression) and 'strong positive' (50% expression) suggest that PD-L1 expression is not a clear dichotomous biomarker and would[10].

4. Approaches to immuno-oncology Drug

In the field of immuno-oncology (IO), drug discovery and development are rapidly advancing towards a pharmacogenomic approach. This approach involves identifying biomarkers in tumor biopsy material to predict the most efficacious therapies for individual patients[11].

A recent retrospective study involving a large cohort of pancreatic cancer patients (n=1,856) demonstrated the significant impact of precision medicine on survival outcomes, especially in cancer types with historically poor prognoses. The study revealed that patients with actionable mutations, including some associated with checkpoint inhibitors, who received matched targeted therapies experienced longer overall survival times compared to those receiving unmatched therapies[12].

For major IO drug families such as anti-PD-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) drugs, the relationship between target expression and treatment response between is complex [24] . Despite the importance of PD-L1 expression as a biomarker, there are reports of treatment response regardless of PD-L1

expression levels. Furthermore, there is uncertainty about the thresholds for defining 'positive' and 'negative' biomarker expression values, particularly for PD-L1. Current definitions, such as 'weak positive' (1-49% specificity) and 'strong positive' (50% specificity) suggest that PD-L1 expression is not a clear dichotomous biomarker and willfor IO treatments that offer increased specificity and reproducibility[13].

Biomarker testing for PD-1/PD-L1, response rates in PD-L-positive and PD-L-negative patients, and emerging biomarkers are areas of ongoing research and development in IO field with efforts focused on increasing the predictive power of biomarkers to improve treatment selection and improve patient outcomes[14].

5. PD-1/PD-L1 Biomarker Assays

Expressed in a number of tumor cell types, the PD-L1 ligand is an important molecular target for half of nearly all immune checkpoint inhibitors (ICPis) approved to date Its binding to PD-1 receptors on T-cells on inhibit their activity against tumor cells. Although PD-L1 is also expressed by normal cells, its upregulation in tumor cells and tumor-infiltrating immune cells protects them from immune responses. Screening patients for tumor cell PD-L1 expression with antibodies to PD-L1. Early studies using nivolumab showed improved responses in PD-L1 positive patients, but later trials also showed responses in PD-L1 negative patients, suggesting PD-L1 synthesis expression alone is not sufficient for treatment selection, whereas pembrolizumab requires PD-L1 production. L1 assays for the treatment of early non-small cell lung cancer Various PD-L1 assays, including companion testing, are available or under development to guide treatment decisions[15].

6. Response Rates in PD-L1-positive and PD-L1-negative Patients

Several examples of PD-L1 negative patients responding to anti-PD-L1 immune checkpoint inhibitors (IO agents) have been reported, with tumor biopsy immunostaining offering a possible explanation[29].Tumor biopsies often express PD-L1 showing a wide spectrum of expression, with no or very low expression in some areas or detectable, whereas others show stable expression and therefore, the patient can be classified as PD-L1-negative based lack of staining depending on the biopsy section, but other tumor areas not tested may show dense PD- L1 expression and even, PD-L1 expression is dynamic, influenced by different biological factors effects, including genetic pathways and immune responses stimulated by IO drugs Other factors contributing to biomarker heterogeneity include disease stage, prior treatments, tumor metastasis status, and drug a it includes use. Consequently, PD-L1 expression does not provide a binary discrimination for treatment response[16].

7. Monoclonal Antibodies (MABs)

Monoclonal antibodies (MABs) are a type of immunomodulatory drug that enables the immune system to fight cancer. Specific proteins in cancer cells or immune cells can be targeted by blocking signals to prevent cancer cell division. MAbs work by stimulating the immune system to attack cancer cells or by helping the immune system attack them. Some MAbs bind to cancer cells and facilitate antibody-dependent cell-mediated cytotoxicity (ADCC), improving recognition by the immune system while others, such as checkpoint inhibitors, inhibit immune response it counteracts the diseases attack on cancer cells[17].

8. Emergent Biomarkers

Tumor mutation burden (TMB), which represents mutations in the tumor genome, is associated with better outcomes for immune checkpoint inhibitors (ICPis). Although many PD-1-resistant tumors exhibit a high mutational burden, studies have yielded mixed results regarding the therapeutic response to TMB, casting doubt on its usefulness in of the hospital[18]. Validated pembrolizumab response biomarkers include tumor-specific PD-L1 expression and major microsatellite instability (MSI-H). Emerging IO-related biomarkers, such

as T-cell inflammatory gene expression profile (GEP) and mutated mismatch repair (MMR) genes, prediction of improved overall response rate and progression-free survival for ICPis Show promise to be developed. Although TMB and inflammatory biomarkers are independently predictive of response, TMB analysis in tissue samples faces challenges such as heterogeneity and assay time dependence, lack of standardization Loss-of-function mutations in the MMR pathway are typical biomarkers work for pembrolizumab treatment choice[19].

1.1 Approved Immune Checkpoint Inhibitor

A. Ipilimumab (Yervoy, Bristol-Myers Squibb)

Type: Human (IgG1)

Target: CTLA-4

Mechanism of Action: Block CTLA-4, releasing the brakes on T-cell inhibition, and promoting T-effector cell proliferation and activation. Selective depletion of T-regulatory cells increases the intratumoral T-effector/T-regulatory ratio, leading to tumor cell death.

Indications: Late stage melanoma, unresectable or metastatic melanoma, adjuvant therapy for melanoma, intermediate and low-risk advanced renal cell carcinoma, advanced colorectal cancer (approved dates so are varied).

B. Tremelimumab

Type: Fully humanized (IgG2)

Target: CTLA-4

Mechanism of action: Similar to ipilimumab.

Indications: Malignant mesothelioma.

C. Nivolumab (Opdivo, Bristol-Myers Squibb)

Type: Human (IgG4)

Target: PD-1

Mechanism of Action: Binds to the PD-1 receptor, blocking its interaction with PD-L1/2 antigens, leading to T-cell proliferation and cytokine secretion.

Indications: Melanoma, non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma (RCC), conventional Hodgkin lymphoma, head and neck squamous cell carcinoma (SSCHN), treatment of helpful in metastatic/recurrent cancer of the head and neck (SSCHN), MSI -H/dMMR metastatic CRC, hepatocellular carcinoma, small cell lung cancer (SCLC), and others (approved dates) various types.

D. Cemiplimab (Libtayo, Regeneron and Sanofi)

Type: Human (IgG4)

Target: PD-1

Mode of Action: Similar to nivolumab.

Indications: Metastatic squamous cell carcinoma of the skin.

E. Pembrolizumab (Keytruda, Merck & Co Inc.)

Type: Human (IgG4)

Target: PD-1

Mode of Action: Similar to nivolumab.

Indications: Advanced melanoma, metastatic NSCLC, recurrent SSCHN, conventional Hodgkin lymphoma, metastatic urothelial carcinoma, unresectable MSI-H or DMMR or metastatic solid tumors others, adenocarcinoma of the stomach or duodenum, etc. (approved dates vary).

F. Avelumab (Bavencio, Merck kGaA)

Type: Human (IgG1)

Target: PD-L1

Mechanism of Action: PD-L1 binds to antigen, blocks its interaction with the PD-1/CD80 receptor, enhances cytotoxic T-cell responses and inhibits NK cell activation of tumor cells.

Indications: Merkel cell carcinoma, urothelial carcinoma, advanced RCC (approved dates vary).

1.2 Approved Immuno-oncology Agents as par Target

A. Alemtuzumab (Lemtrada; Campath, Genzyme)

Type: Humanized (IgG1)

Target: CD52

Mechanism of Action: Selective for CD52, resulting

in rapid and prolonged depletion of CD52-positive B-T cells, although the exact mechanism is not fully understood.

Indications: Chronic B-cell lymphocytic leukemia (B-CLL).

B. Rituximab (Rituxan; Mabthera, Genentech)

Type: Chimeric (IgG1)

Target: CD20

Mode of Action: CD20 on B lymphocytes binds antigen, causing lysis and death of B-lymphocytes.

Indications: CD20-positive non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL), follicular lymphoma, Wegener's granulomatosis, microscopic polyangiitis, pemphigus vulgaris.

C. Tositumomab (Bexxar, GlaxoSmithKline)

Type: Murine (IgG2a)

Target: CD20

Mode of Action: CD20 on B lymphocytes binds antigen, causing lysis and death of B-lymphocytes.

Indications: Non-Hodgkin lymphoma.

C. Obinutuzumab (Gazyva/Gazyvaro, Roche)

Type: Humanized (IgG1)

Target: CD20

Mode of Action: CD20 on B lymphocytes binds antigen, activates intracellular death signaling pathways and induces antibody-dependent cellular cytotoxicity (ADCC).

Indications: Chronic lymphocytic leukemia (CLL), follicular lymphoma, naïve CLL are treated with Imbruvica.

1.3 Combination Therapies

The combination of immunomodulatory drugs (ICPis) with other therapeutic modalities has received considerable interest in terms of high response rates and durability. Although a single therapy may produce dramatic responses in some patients, only limited benefit is achieved. The combination of ipilimumab and nivolumab is FDA-approved for advanced melanoma and advanced renal cell carcinoma (RCC). Clinical trials are investigating the potential in other cancers. Furthermore, the combination of PD-1/PD-L1 inhibitors with CAR-T cell therapy shows promise for the development of small inflammatory tumors. The aim of adding IO drugs to chemotherapeutic regimens is to achieve additive efficacy, and reduce co-toxicity. The FDA has approved several combinations, such as pembrolizumab plus pemetrexed platinum and atezolizumab plus bevacizumab/carboplatin/paclitaxel, for non-small cell lung cancer, reflecting conventional treatment[20].

1.4 Cost of immuno-oncology therapies

Immuno-oncology therapies carry significant costs, with estimated global costs of non-small-cell lung cancer (NSCLC) treated with selected immunosuppressive drugs (ICPis); use of the U.S. $80 billion a year from £100,000 per patient per year IO agents are superior, putting a strain on health systems[21]. In the UK, the National Institute for Healthcare Information (NICE) assesses the cost-effectiveness of alternative therapies, but many IO treatments are beyond cost-effective The Institute for Clinical Economic Review shows a change in quality. Meeting the life-year (QALY) threshold will require substantial reductions in primary immunotherapy. As a result, NICE does not recommend routine use of some IO drugs in the NHS[22-25].

9. Conclusion

Immuno-oncology (IO) represents a revolutionary approach to cancer treatment, but its full potential is not yet realized. Challenges include optimizing treatment, monitoring toxicity, and integrating IO into quality care while addressing cost concerns. Immune checkpoint inhibitors (ICPis) such as pembrolizumab and ipilimumab have shown promise but can cause significant toxicity, prompting investigation into long-term monitoring of toxicity and side effects Furthermore, new IO drug candidates have been developed target changes in T-cell function. they focus on methods such as A and LAG-3. The integration of existing IO agents into conventional

therapies is also gaining momentum, with studies showing promising results, further underscoring the evolving state of IO therapy.

Conflict of Interest: None

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