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Review Paper

Review on Immuno-Oncology agents for Cancer Therapy

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ABSTRACT

Until recently, cancer therapy comprised of four main types of treatment: surgery, radiotherapy, chemotherapy and targeted therapy. Over the past decade, immuno-oncology (IO) has emerged as a novel and important approach to cancer treatment through the stimulation of the body's own immune system to kill cancer cells. This newly recognised method of treating cancer is rapidly developing, with many accelerated approvals by the US Food and Drug Administration and European Medicines Agency in 2019. Several therapeutic classes have emerged within IO, and are the focus of this review article. In particular, the immune checkpoint inhibitors have had remarkable success across multiple malignancies, and are the most well-established therapeutic class of IO agents to date. Biomarker testing for the programmed death-ligand 1 (PD-L1) checkpoint target has been developed and is now obligatory before treatment with pembrolizumab (Keytruda, Merck) when used for non-small-cell lung carcinoma, gastric cancer, head and neck squamous cell carcinoma and cervical cancer, as well as before treatment with atezolizumab (Tecentriq, Roche) when used for urothelial carcinoma. However, ambiguity remains as to the relevance of PD-L1 expression for checkpoint inhibition therapy for other tumour types. More recently, combining IO agents with conventional therapies has been evaluated with some significant improvements in patient outcomes. While IO agents are rapidly changing the standard of care for people with cancer, there are still many challenges to overcome in terms of managing their toxicities and ensuring that healthcare systems, such as the NHS, can afford the high cost of these therapies. The IO pipeline also includes chimeric antigen receptor T-cell therapies and cancer vaccines, both of which show great promise for the future but have their own unique toxicity and cost-effectiveness issues.

INTRODUCTION

Cancer incidence rates have steadily increased over the past 20 years, while mortality rates have shown a considerable decline. Although significant variation in survival rates is still observed across cancer types (i.e. there are more 200 distinct diseases recognised), for most types,

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survival is improving owing to earlier diagnosis and improved treatments. Treatment has undergone a slow evolution from its start in the 1800s, with the sequential development of four main recognised modes of treatment. The first was surgery, which was made possible after the discovery of general anaesthetics in the late 1800s This was a revolutionary development because it was the first time the disease could be completely eradicated as long as the tumour was small and well-defined. The second development was radiotherapy, established at the end of the 19th century, which utilises X-rays and/or G-rays to damage the DNA within tumour cells, thus blocking essential biochemical processes and leading to cell death. This concept of using modern structural biology and drug discovery methods to produce small molecules, proteins, antibodies and even cellular therapies designed to target unique biomarkers associated with tumour cells, but not healthy cells, is now considered to be the 'gold standard' approach for discovering new cancer treatments. Currently, four major treatment modes — surgery, radiotherapy, chemotherapy and targeted agents — are frequently used in combination to ensure that all cancer cells are eradicated from the body. During the past decade, the first immuno-oncology (IO) treatments (e.g. checkpoint inihibitors) have emerged, which work by harnessing the body's own immune system to kill tumour cells. They are presently showing great promise in the clinic, and are the main focus of this review.

History of immuno-oncology:

It has long been known, but is now increasingly appreciated, that tumour cells can be recognised and disabled by the immune system. Some tumours show evidence of spontaneous regression early in their development, suggesting that the immune system may be capable of recognising and eliminating early-stage tumour cells. Observation of spontaneous remissions in patients led to the foundation of the area of IO. A spontaneous remission is defined as a reduction in severity of, or disappearance of, the signs and symptoms of a disease, without any apparent cause and in the absence of treatment. This is most often noted in patients who have recently had acute infections, especially when this results in fever which appears to stimulate the immune system. It is now recognised that, in some cases, the immune system is capable of completely eliminating a tumour. Spontaneous remissions have been observed in most cancer types, but most frequently in advanced melanoma, renal cell carcinoma (RCC) and urothelial carcinomas, although the phenomenon has also been reported in breast cancer, neuroblastomas, some sarcomas and embryonal cancers. William Coley was the first to investigate the potential for IO, and successfully treated malignancies based on immune stimulation in the 1890s. After discovering that cancer patients who contracted post-surgical infections seemed to improve faster than those who did not, he investigated the use of bacteria to stimulate and enhance the body's natural immune response to fight cancer. Through these studies, he later developed Coley's toxin, which was based on attenuated bacteria and is thought to be the first known IO therapy. A later development involved the Bacillus Calmette-Guerin (BCG) vaccine, originally produced in the early 1900s for use against tuberculosis (TB), and first used therapeutically for TB in the 1920s. However, its role in cancer therapy dates back to 1929 when a reduced incidence of cancer among patients with TB was observed at autopsy. Experiments revealed that BCG produced a profound stimulation of the mononuclear phagocyte system (also known as the reticuloendothelial system), which was recognised as an important defense against cancer. Furthermore, it was observed that neonates who had been immunised with BCG had

a significantly lower incidence of leukaemia later in their lives. This background and basic understanding of IO sparked an interest in the use of BCG for other types of malignancies, in particular bladder cancer. Early investigations demonstrated responses in patients with melanoma metastatic to the bladder when treated with intralesional BCG. In light of this success, work in animal models led to publication of the results of the first successful clinical trial of intravesical BCG in patients with recurrent bladder cancer. It is now understood that intravesicularly adminstered BCG attaches to bladder tumours and urothelial cells via specific fibronectin and integrin receptors. Following internalisation by macropinocytosis, the mononuclear phagocyte system is stimulated by the BCG, inducing a local inflammatory response characterised by the infiltration of granulocytes, macrophages and lymphocytes. Important elements of the humoral immune response to BCG include the interleukins (ILs) IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumour necrosis factor alpha (TNF-a) and interferon gamma. More recently, studies have shown that BCG contains high levels of CpG oligodeoxynucleotide motifs that are known to induce the TNF-related apoptosis-inducing ligand (TRAIL) through IFN production. Intravesical BCG is still indicated for the treatment and prevention of recurrence of some types of non-invasive bladder cancers.

What are the types of immunotherapy:

Several types of immunotherapy are used to treat cancer. These include:

- **Immune checkpoint inhibitors**, which are drugs that block immune checkpoints. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more strongly to cancer.

- **T-cell transfer therapy**, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein.

T-cell transfer therapy may also be called adoptive cell therapy, adoptive immunotherapy, or immune cell therapy.

- **Monoclonal antibodies**, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy.

Monoclonal antibodies may also be called therapeutic antibodies.

- **Treatment vaccines**, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.

- **Immune system modulators**, which enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, whereas others affect the immune system in a more general way.

How does immunotherapy work against cancer:

As part of its normal function, the immune system detects and destroys abnormal cells and most likely prevents or curbs the growth of many cancers. For instance, immune cells are sometimes found in and around tumors. These cells, called tumor-infiltrating lymphocytes or TILs, are a sign that the immune system is responding to the tumor.

People whose tumors contain TILs often do better than people whose tumors don't contain them.

Even though the immune system can prevent or slow cancer growth, cancer cells have ways to avoid destruction by the immune system. For example, cancer cells may:

- Have genetic changes that make them less visible to the immune system.
- Have proteins on their surface that turn off immune cells.
- Change the normal cells around the tumor so they interfere with how the immune system responds to the cancer cells

Which cancers are treated with immunotherapy:

- Immunotherapy drugs have been approved to treat many types of cancer. However, immunotherapy is not yet as widely used as surgery, chemotherapy, or radiation therapy. To learn about whether immunotherapy may be used to treat your cancer, see the PDQ® adult cancer treatment summaries and childhood cancer treatment summaries.

How is immunotherapy given:

Different forms of immunotherapy may be given in different ways. These include:

- **Intravenous (IV)** The immunotherapy goes directly into a vein.
- **Oral** The immunotherapy comes in pills or capsules that you swallow.
- **Topical** The immunotherapy comes in a cream that you rub onto your skin. This type of immunotherapy can be used for very early skin cancer.
- **Intravesical** The immunotherapy goes directly into the bladder.

Immunotherapy is working:

- You will see your doctor often. He or she will give you physical exams and ask you how you feel. You will have medical tests, such as blood tests and different types of scans. These tests will measure the size of your tumor and look for changes in your blood work.

Future of immunotherapy:

This area appears to be moving away from the development of agents selective for a given cancer type. IO agents are now rarely approved for one particular type of cancer; instead, there is a focus on the pathways involved and the expression of specific biomarkers in tumours, regardless of their origin or location (i.e. 'tissue agnostic' therapies). This pan-cancer approach is evident with the first tumour-agnostic approval of Keytruda by the FDA, in 2017, for patients with unresectable or metastatic solid tumours based on their MSI-high and dMMR status, as opposed to the location or origin of the tumour. Merck, the company which developed Keytruda, is now seeking a second pan-cancer indication against the TMB biomarker, aiming to widen patient access still further. There has been a similar trend towards a tumour-agnostic approach in the small-molecule oncology area; for example, in the past two years, the kinase inhibitors larotrectinib and entrectinib have been granted accelerated approval by the FDA for use in patients with any solid tumour-type that has the NTRK fusion mutation. To date, two comprehensive studies of the global IO landscape have been conducted. Over a one-year period, between September 2017 and August 2018, it was established that the global IO pipeline had increased by 67%, with cell therapy showing the most significant increase of 113% in the number

of active agents, followed by other immunomodulatory (e.g. aldesleukin and interferons; 79%) and T-cell-targeted immunomodulatory therapies (76%). Importantly, the number of IO targets also increased by 50% from September 2017 to August 2018, suggesting that there could be significant broadening of the IO landscape in the future. Both reviews concluded that, of the many IO agents in clinical development, a large percentage are concentrated on only a few targets (e.g. PD-1, PD-L1 and CTLA4)[9]. In addition to the five antibodies already granted FDA and EMA approval, the UK-based Cancer Research Institute has identified 164 agents in development targeting either PD-1 or PD-L1, with 50 of these at the clinical stage. This suggests that there is significant duplication in product development, and raises concerns as to whether the current approach of focusing on a small number of biomarker targets is stifling further innovation. It is noteworthy that the number of agents being developed against non-tumour-specific antigens actually decreased during the same period, consistent with the suggestion that IO is becoming too focused on a few specific targets. However, there is growing interest and enthusiasm for the IO area in both the pharmaceutical industry and academia. In addition, clinical data suggest that IO agents have significant potential for the future and may lead to several breakthrough treatments that could improve the standard of care in many different cancer types.

Common immunotherapy side effects:

The most common side effects of immunotherapy include:

Skin reactions:

Skin redness, blistering, and dryness are common reactions to immunotherapy. Skin on the fingertips may crack. Skin may also become more sensitive to sunlight . A lot of scratching can break the skin, making it more prone to infections. Inflammation around the nails can make grooming, dressing, and other activities painful or difficult. Read more about managing and treating skin irritations and reactions.

Flu-like symptoms. Fatigue (feeling tired), fever, chills, weakness, nausea (feeling sick to your stomach), vomiting (throwing up), dizziness, body aches, and high or low blood pressure are all possible side effects of immunotherapy. They are especially common in non-specific immunotherapy and oncolytic virus therapy. It is very important to stay hydrated when experiencing these symptoms. Seek medical attention if you are unable to keep any liquids down, and talk with your doctor about how to manage these side effects. Many side effects will go away on their own, but others can be very serious and require attention right away.

Other possible side effects you may experience include:

- Muscle aches
- Shortness of breath (trouble breathing)
- Swelling of legs (edema)
- Sinus congestion
- Headaches
- Weight gain from retaining fluid
- Diarrhea
- Hormone changes, including hypothyroidism, which is when the thyroid gland does not make enough thyroid hormones and can cause fatigue and weight gain

- **Cough:**

It is important to note that there can be other side effects that are not listed here. Talk with your health care team about what side effects you can expect, who to contact, and what to do if you have unexpected side effects. Learn more about managing physical side effects. Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight cancer. It uses substances made by the body or in a laboratory to improve, target, or restore immune system function. Your doctor may recommend immunotherapy as the only treatment. Or it may be given after or at the same time as another treatment, such as chemotherapy, radiation therapy, or surgery.

What is the current research in immunotherapy:

Researchers are focusing on several major areas to improve immunotherapy, including:

- **Finding solutions for resistance.**

Researchers are testing combinations of immune checkpoint inhibitors and other types of immune therapy, targeted therapy, and radiation therapy to overcome resistance to immunotherapy.

- **Finding ways to predict responses to immunotherapy.**

Only a small portion of people who receive immunotherapy will respond to the treatment. Finding ways to predict which people will respond to treatment is a major area of research.

- **Learning more about how cancer cells evade or suppress immune responses against them.**

A better understanding of how cancer cells get around the immune system could lead to the development of new drugs that block those processes.

- How to reduce the side effects of treatment with immunotherapy

Advanced Cancer Therapy :

The earliest evidence of cancer treatment can be traced back to an ancient Egyptian medical text, written around 3000 BC and known widely as the 'Edwin Smith Papyrus', that described the cauterization of breast tumors for which, according to the text, there was no cure. The situation is very different now, as, depending on breast cancer subtype, stage, and demographic factors, the 5- year survival rates for this disease can surpass 90% in developed countries. For cancer types that are responsive to therapy, including certain subtypes of breast, blood, and prostate malignancies, patients now face the management of a chronic disease, rather than a fatal one, owing to the rapid advances in clinical oncology over recent decades. Similarly, the prognosis for several other cancer types has also been improving. For example, patients with melanoma, which used to be considered a deadly disease, have much better prospects thanks to the breakthroughs in targeted and immune-based therapies. These advances reflect the focus placed on cancer research and oncology by governments, funders, and research institutes across the globe over the past several decades. In the USA, 2021 marks the 50th anniversary of the signing of the National Cancer Act into law, which marked the beginning of a concerted effort to address cancer as a leading cause of death in the USA at the federal level. The National Cancer Program that arose from this initiative resulted in a profound institutional reorganization within the National Institutes of Health, with the overarching goal of developing the infrastructures required 'for the treatment, cure, and elimination of cancer'. Other

countries and international agencies also adopted cancer-focused initiatives over the years, including, for example, the PRIME scheme of the European Medicines Agency, which supports the development of medicines that target an unmet medical need, including cancer, through accelerated planning, evaluation, and approval processes. Thus, substantial progress has been made across first-line cancer therapy modalities. Surgery continues to be a first-line treatment for many cancer types, but it now includes precision and minimally invasive surgery, molecular imaging support, and, more recently, robot- or artificial intelligence–assisted surgical procedures. The clinical use of one of the most widely used treatment modalities, chemotherapy, has been improved through better-dosing regimens, neoadjuvant or adjuvant administration, and combination therapies. Similarly, radiation oncology has been advanced through precision radiotherapy. First-line recommendations depend on the cancer type and stage at diagnosis and have continued to be modified as new therapeutic modalities have become available. The advent of targeted therapy and immunotherapy has revolutionized the treatment of cancer, especially with the development and availability of sophisticated diagnostic and molecular characterization technologies. Among these, '-omics' techniques stand out for increasingly enabling a more precise and granular molecular characterization of cancer types and subtypes and the identification of biological correlates of response to specific therapies, thereby enriching the roster of biomarkers at the disposal of clinicians. Targeted therapies have swiftly taken a prominent position in cancer research and clinical oncology in recent decades, thanks to the molecular insights into oncogenic processes and mechanisms gained from fundamental research and technological development. A key example of how basic research on oncogenic alterations translated into substantial clinical benefits for a large number of patients is BCR-ABL1 tyrosine-kinase inhibitors for chronic myeloid leukemia. The first BCR-ABL1 tyrosine-kinase inhibitor was discovered through drug screens in 1992, and in 2001 it became the first-line therapy with long-term remission rates for BCR-ABL– driven chronic myeloid leukemia1; second-generation tyrosine-kinase inhibitors, rationally designed to circumvent acquired resistance, earned approval from the US Food and Drug Administration as frontline therapies only a decade later. More recently, the announcement of the two first-in-class inhibitors of the mutant kinase KRAS G12C was a milestone in the decades-long efforts to study and treat tumors bearing these, up-to-now considered undruggable, KRAS mutations2. However, not every effort in precision oncology and targeted therapy is yielding similarly positive results, especially given the issue of adaptive and acquired resistance, a complication of therapy that a large part of the cancer research community is striving to address. It should also be noted that advances in sophisticated cancer therapeutics are sometimes associated with a high financial burden for patients, a pressing societal issue tied to the complexities of addressing the challenge of cancer.

Current Research:

As of September 2017, 58% of all clinical trials evaluating IO therapies were combination trials, 82% of which involved either another IO agent, targeted therapy, and/or a cytotoxic agent, while around 16% of combination trials involved PD-L1 antagonists and 20% CTLA-4 inhibitors. However, as of September 2019, there were 1,469 more active clinical trials evaluating PD-1/PDL1 mAbs alone or in combination with other agents, with 76% of these active trials investigating combination therapies. NSCLC, melanoma, and non-Hodgkin's lymphoma have been at the

forefront of IO research since its infancy, although, in recent years, interest in other malignancies such as renal, pancreatic, and advanced (metastatic) cancer has significantly increased. However, since 2014 the average number of planned enrolments has declined from an average of 429 to 129 patients per trial, reflecting the shift in focus from major tumour types (e.g. melanoma and breast cancer) to rarer cancers with a significantly smaller eligible population. Current clinical research efforts are focussed largely on combining recently approved IO agents with either another IO agent or an existing treatment (i.e. chemotherapy or radiotherapy). Data from 2018 show that there are more than 1,700 clinical trials worldwide assessing combinations of anti-PD-1/PD-L1 agents with other cancer therapies, including anti-CTLA-4 agents (n=339), chemotherapy (n=283), and radiotherapy (n=114). This shift from monotherapies to combination therapies within clinical trials has resulted in 14 approvals of combination therapies by the FDA, with the three most common being PD1/PD-L1 inhibitors in combination with chemotherapy, CTLA-4 inhibitors and vascular endothelial growth factor (VEGF)-targeted therapies (as of September 2019). T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) is an immune receptor present on the surface of some T-cells and natural killer (NK) cells. Similar to PD-1, it is an inhibitory checkpoint that is upregulated in multiple cancer types (e.g. melanoma, colon, and renal cancer) and also plays a role in the activation and maturation of T-cells and NK cells. The associated ligand, poliovirus receptor (PVR), is highly expressed on the surface of dendritic, endothelial, and some tumor cells.

CONCLUSION:

IO is a fundamentally different approach to cancer therapy and is redefining the way that both solid and haematological tumours are treated. However, this new treatment paradigm is still in its infancy, and there is a long way to go in optimising the use of these novel therapies, minimising their toxicities and learning how to integrate them into the current standard of care. Furthermore, given their high cost, there are challenges ahead in incorporating them into healthcare systems in an economically sustainable manner, while increasing availability for patients. The investigation of new targets and pathways in the IO area is vital to developing new therapies; however, it is important to note that combinations of presently approved IO agents with existing chemotherapeutic or biological agents are also generating significant interest. For example, a study evaluating a combination of an IO agent with an antibody-drug conjugate has reported encouraging results.

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