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A Review On Immuno-Oncology Agents For Cancer Therapy

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Abstract :

TheUntil recently, cancer therapy comprised 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 immune system to kill cancer cells. This newly recognized method of treating cancer is rapidly developing, with many accelerated approvals by the US Food and Drug Administration and the 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. 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.

keywords- **Immune-Oncology, Advanced Cancer Therapy, Future Of Immunotherapy.**

I. 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 than 200 distinct diseases recognized), for most types, 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 recognized modes of treatment. The first was surgery, which was made possible after the discovery of general anesthetics 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 tumor was small and well-defined. The second development was radiotherapy, established at the end of the 19th century, which utilizes X-rays and/or G-rays to damage the DNA within tumor cells, thus blocking essential biochemical processes and leading to cell death. The third development, chemotherapy, was discovered in the 1940s, during World War II, when it was observed that individuals exposed to mustard gas suffered myelosuppression. Clinicians speculated that patients with proliferative diseases (e.g. leukemia) might benefit from treatment with agents of this type that kill highly proliferating cells. Crucially, the introduction of the first chemotherapy agents (analogs of nitrogen mustard gas) meant that cancers that were more complex or had

metastasized and could not be successfully treated by surgery or radiotherapy could now be addressed. Furthermore, chemotherapy agents have since been developed that work at different stages of the cell cycle and can be used in combination to prevent the development of resistance. The fourth development was targeted cancer therapies (also known as precision therapies). This was established with the discovery of imatinib (Glivec; Novartis) in the late 1990s — a small-molecule kinase inhibitor targeted to the mutant BCR-ABL protein present in the tumor cells of patients with chronic myeloid leukemia (CML), but not in their healthy cells. 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 tumor 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 have emerged, which work by harnessing the body's immune system to kill tumor cells. They are presently showing great promise in the clinic, and are the main focus of this review. Immune checkpoint proteins are found on the surface of T-cells and act as regulators of the immune system. They are crucial for self-tolerance and prevent the immune system from attacking the body's cells indiscriminately, thus allowing a distinction to be made between 'self' and 'non-self'. Immune checkpoints also play a vital role in preventing uncontrolled immune responses by modulating the duration and amplitude of a physiological immune response, thus preventing collateral damage, which is why the term ‘off-switch’ is sometimes used to describe their role. It is known that tumors adopt certain immune checkpoint pathways as a mechanism to evade an immune response towards them. For example, some tumor cell types express these proteins on their surface to disguise themselves as ‘self’, allowing them to go unnoticed by the immune system and promoting tumor progression.

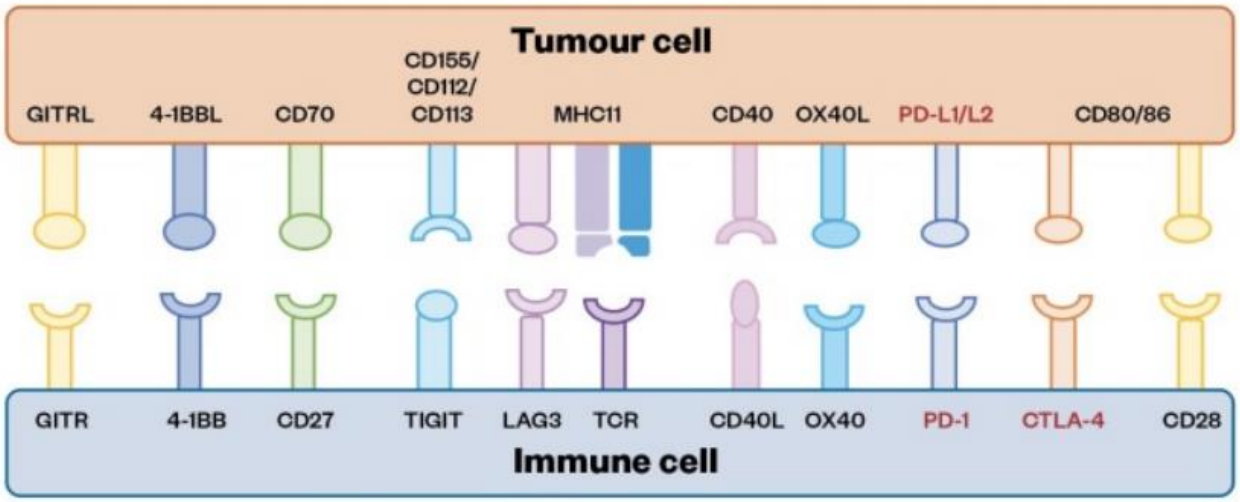

Fig.1: Tumor Cell / Immune Cell

❖ **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 tumors show evidence of spontaneous regression early in their development, suggesting that the immune system may be capable of recognizing and eliminating early-stage tumor 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 recognized that, in some cases, the immune system is capable of eliminating a tumor. 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 recognized as an important defense against cancer. Furthermore, it was observed that neonates who had been immunized with BCG had a significantly lower incidence of leukemia 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 the 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 administered BCG attaches to bladder tumors and urothelial cells via specific fibronectin and integrin receptors. Following internalization by macropinocytosis, the mononuclear phagocyte system is stimulated by the BCG, inducing a local inflammatory response characterized by the infiltration of granulocytes, macrophages, and lymphocytes.

- **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/PD-L1 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.

❖ 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 tumors, regardless of their origin or location (i.e. 'tissue agnostic' therapies). This pan-cancer approach is evident with the first tumor-agnostic approval of Keytruda by the FDA, in 2017, for patients with unresectable or metastatic solid tumors based on their MSIhigh and dMMR status, as opposed to the location or origin of the tumor. Merck, the company that 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 tumor-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 tumor-type that has the NTRK fusion mutation. To date, two comprehensive studies of the global IO landscape have been conducted. Over one year, 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). 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-tumor-specific antigens 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

❖ Conclusion :

IO is a fundamentally different approach to cancer therapy and is redefining the way that both solid and hematological tumors are treated. However, this new treatment paradigm is still in its infancy, and there is a long way to go in optimizing the use of these novel therapies, minimizing 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. ICPis have been the focus of the recent revolution in IO, with two main antibodies (i.e. pembrolizumab and ipilimumab) receiving multiple approvals for PD-1/PD-L1 and CTLA-4 blockade, respectively. Owing to their success, there has been significant interest in combining IO agents with conventional therapies. However, despite their promising efficacy in the clinic, the ICPis produce significant toxicities in some patients. These adverse effects are frequent, but different from those seen with conventional cancer therapies. Therefore, clinical research is beginning to focus on managing and predicting these toxicities and monitoring long-term outcomes. This should lead to guidelines on how to manage these new therapies and should encourage clinicians to use them as early as possible in treatment pathways. While the pipeline of ICPis is ever-expanding, the introduction of cancer vaccines and CAR-T cell therapies is also rapidly growing. In particular, there is a strong emphasis on developing new IO agents that can modulate T-cell activity through signaling pathways (e.g. VEGF-A, LAG-3, and IDO-1), to increase understanding of how modulation of these pathways can restore the body's natural ability to fight cancer.

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