

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 recognized 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^[1]. 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 tumors 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 those 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: biomarkers; cancer; immune checkpoint inhibitors; immuno-oncology; oncology

INTRODUCTION

Cancer incidence rates have steadily increased over the past 20 years, while mortality rates have shown a considerable decline^[1]. Although significant variation in survival rates is still observed across cancer types (i.e. there are more 200 distinct diseases recognized), for most types, survival is improving owing to earlier diagnosis and improved treatments^[2,3]. 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 1800s⁴. This was a revolutionary development because it was the first time the disease could be completely eradicated as long as the tumors was small and well-defined^[2]. 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. The third development, chemotherapy, was discovered in the 1940s, during World War II, when it was observed that individuals exposed to mustard gas suffered myeloma suppression^[4]. Clinicians speculated that patients with proliferative diseases (e.g. leukaemia) might benefit from treatment with agents of this type that kill highly proliferating cells. Crucially, introduction of the first chemotherapy agents (analogues of nitrogen mustard gas) meant that cancers which 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 (Gleevec; Novartis) in the late 1990s — a small molecule kinase inhibitor targeted to the mutant BCR-ABL protein present in the tumour cells of patients with chronic myeloid leukaemia (CML), but not in their healthy cells^[5]. 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 inhibitors) have emerged, which work by harnessing the body's own immune system to kill tumour cells^[6]. 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 own 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 tumours adopt certain immune checkpoint pathways as a mechanism to evade an immune response towards them^[7]. For example, some tumour cell types express these proteins on their surface to disguise themselves as 'self', allowing them to go unnoticed by the immune system and promoting tumour progression^[8]. PD-1 (programmed death 1) is an example of an inhibitory checkpoint receptor protein found on the surface of T-cells that normally acts as an 'off-switch' after interaction with the PD-1 ligand (PD-L1), a protein expressed on the surface of normal cells. However, PD-L1 is expressed by many types of tumour cells and up regulated

in some, thus activating the 'off-switch' and protecting the malignant cells from an immune attack^[9,10]. Immune checkpoint inhibitors (ICPis), such as the anti-PD-1/PD-L1 agents, prevent the interaction between PD-L1 on tumour cells and PD-1 on T-cells, allowing the immune system to launch an antitumor response. Many observers believe that, over the next decade, IO agents could become the fifth acknowledged cancer treatment modality^[11]. Some of the main ligands and receptors present on the surface of tumour and immune cells that are targets for approved and emerging.

Classification of immuno-oncology agents

The categorisation of IO agents is challenging and there is significant crossover and ambiguity with emerging agents. The classification devised and utilised throughout this review is represented in Tables 1–4. For example, ICPis (see Table 1) are sometimes classified separately to monoclonal antibodies (maybes; see Table 2), yet the ICPis are, themselves, monoclonal antibodies. The Cancer Research Institute takes two broad approaches to classification based on treatment type or cancer type^[12,13]. Few observers employ the three very broad categories that have emerged over the years: non-specific cytokines, cancer vaccines and mAbs^[14]. Another approach is to classify IO agents from a mechanistic perspective as 'active' or 'passive'. However, this is perhaps too simplistic, as it does not properly reflect the many possible complex drug–host–tumour interactions. In this review, passive naked maybes, such as the ICP is and those directed at other external and internal cellular targets are grouped adjacently, while conjugated mAbs (i.e. antibody–drug conjugates and immunotoxins and active therapies) classified separately. The mAbs form the largest and best-characterized group of passive IO agents. Within this broad group are the ICP is which constitute the most promising emerging area at present. Several active immunotherapies are licensed as IO agents and these fall into four groups: immunomodulatory agents, cancer vaccines, oncolytic viruses and CAR-T cell therapy. The latter is a newly emerging therapy that is generating significant interest. It involves the collection of T-cells from cancer patients followed by their ex vivo modification and re-administration to the same patient. Currently there are only two approved CAR-T cell therapies (Yescarta, Kite Pharma; and Kymriah, Novartis), although many more are in the pipeline. Cost of immuno-oncology therapies There are significant cost implications associated with IO-based therapies. For example, the one-year global cost of treating NSCLC with selected ICPis has been estimated at over US\$80 billion¹². The estimated cost per patient per year for a variety of IO agents is over £100,000, which places significant pressure on healthcare systems^[15]. Costs for implementing these newer targeted therapies have escalated dramatically, and the duration of treatment has also lengthened because many cancer types are increasingly being treated as chronic rather than acute diseases. In the UK, the National Institute for Health and Care Excellence (NICE) is the organisation responsible for determining whether new treatments are cost-effective for the NHS. The cost of a new therapy is evaluated for its clinical effectiveness using a standardised measurement known as a quality-adjusted life year (QALY). In order to be deemed cost-effective for the NHS, a therapy should cost no more than £20,000–30,000 per QALY gained, or £50,000 for end-of-life therapies. New IO agents are increasingly exceeding these thresholds, resulting in rejection by NICE and reduced access for patients^[16]. The Institute for Clinical and Economic Review, a US-based nonprofit organisation providing comprehensive clinical and cost-effectiveness analyses of treatments, tests, and procedures, has studied the cost-effectiveness of the three leading immunotherapies (i.e. atezolizumab, nivolumab and pembrolizumab) and concluded that each therapy would need to be discounted by 31%–68% to reach the QALY threshold. Taking this into account, NICE has stated that nivolumab cannot be recommended for routine use in the NHS with estimated QALYs of £58,791 and £78,869 versus paclitaxel and docetaxel, respectively, for treatment for urothelial cancer after cisplatin chemotherapy. NICE has also recommended that use of these agents should not be supported by the Cancer Drugs Fund (a 'back-up' government-sponsored fund allowing patients to obtain expensive cancer treatments through the NHS) because they do not have the potential to be cost effective¹¹⁸. Although the cost of IO agents tends to exceed QALY thresholds, consideration of the cost-effectiveness of a drug or technology is not the sole basis for decision making; clinical effectiveness and multiple patient factors are typically assessed in parallel^[16]. Often, when a new treatment strategy is evaluated, it is more clinically effective than many existing treatments, but is significantly more expensive. In this case, further economic evaluation is carried out, for example establishing the magnitude of the incremental cost-effectiveness ratio, for which an upper threshold set by NICE may not be exceeded. A decision can then be made as to whether the increase in cost is associated with an enhancement in clinical effectiveness that represents value for money¹²⁰. Currently, there are several indications for IO agents recommended by NICE based on both cost- and clinical-effectiveness (e.g. melanoma, UC, RCC, NSCLC, lymphoma and breast cancer). Many pharmaceutical industry analysts have suggested that, moving forward, there should be a greater emphasis on the value and affordability of novel IO agents, rather than on generating larger numbers of potential candidates of similar therapeutic activity. There is no easy solution to this problem as it is difficult to curtail the enthusiasm of the biotechnology sector; however, it is evident that a longer-term more-sustainable research and development strategy for novel IO therapies is required. Precision medicine approaches have the potential to reduce the costs and risks.

associated with drug discovery and development, particularly for the clinical trials that are typically the most expensive stage of the process. The cost-saving comes from stratifying patients into smaller subsets and identifying groups that are more likely to respond, thus reducing the sizes of clinical trials and substantially reducing costs. Identifying those who are more likely to respond is also more beneficial for patients. For example, an analysis of 676 phase III–IV clinical trials of NSCLC over a 14-year period found that the use of a biomarker resulted in a 26% reduction in risk-adjusted drug development costs¹³⁰. Another option to reduce costs would be to modify treatment pathways to utilise IO agents earlier in a patient's cancer journey, thus potentially reducing costs from treating severe ADRs often associated with conventional chemotherapy and radiotherapy, and the subsequent hospitalization that many patients requirement

CURRENT CHALLENGES

The two most important challenges for IO therapies are the inability to accurately predict patient response and managing toxicities. However, the lack of information on relevant biomarkers and the high cost of research, development and treatment are also significant concerns^[16]. Some observers also argue that future research should be directed towards reducing toxicity.

Unpredictability of clinical efficacy

Newly developed agents tend to have unpredictable efficacies. There are several possible reasons for these differences in clinical responses, including the presence of different gene mutations and varying degrees of activity of specific signalling pathways in individual patients. The overall aim is to produce consistently effective agents in most patients across the majority of cancer types. Developments appear to be moving in this direction with the recent expansion of indications. For example, in 2018, the EMA expanded the marketing authorisation for pembrolizumab by adopting a new indication for the adjuvant treatment of stage III melanoma. It has been suggested that the longstanding use of chemotherapy as first-line treatment for the majority of cancer types may be impeding the development and use of IO agents that are not yet widely approved for first-line use. At present, they are administered to patients who are immuno compromised owing to prior chemotherapy, so the restoration of antitumour immune function under these conditions is challenging. Therefore, it has been postulated that greater efficacies might be achieved if IO agents are utilised earlier in the treatment plan in order to utilise the full capability of the immune system. Another challenge is that IO agents should ideally be directed against tumour-specific antigens solely expressed by tumour cells in order to minimise off-target effects. There would be significant clinical and economic benefits if accurate predictive biomarkers could be identified and developed, as only patients who are likely to have the greatest response would be treated. However, as seen with PD-L1 expression assays, at present there is a lack of reliability in using IO-related biomarkers to direct treatment

Cost of immuno-oncology therapies

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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)¹³¹. 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^{[7][8][9]}. 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 tumouragnostic 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 mutation¹⁷⁴. 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 interferon^γ; 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)^{27,115}. 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 type.

CONCLUSION

Cancer immunotherapy has dramatically changed survival and quality of life for patients. However, not all cancers are equal, and very few predictors of response and toxicity currently exist. Despite the rapid advances made in the field, immuno-oncology is still in its relative infancy, with numerous challenges and hurdles yet to be overcome. Over time, a realization grew that the standard tools used to assess choice of treatments in the era of chemotherapy and targeted therapies might not be valid for the new immunotherapies. As an example, the Response Evaluation Criteria in Solid Tumors (RECIST) used to assess response to treatments

were modified to create it, which accounts for the novel patterns of response seen during immunotherapy, including tumour pseudo progression ECIST. In the same way that TNM staging has been crucial in guiding treatments in the era of chemotherapy, novel tools are required in the era of cancer immunotherapy. The Immunoscore has already been validated as adding important prognostic information to TNM staging in colon cancer. The fact that T cells are currently widely recognized as the key mediators of antitumour efficacy with treatment suggests that use of the Immunoscore is an attractive option to help guide treatment selection in other cancer types as well. Still, that option does not exclude the possible use of additional parameters that might provide further insights into the specifics of each case.

It is becoming more challenging to increase the efficacy of combination therapies already established in clinical practice. In metastatic melanoma, combined CTLA-4 and PD-1 blockade has achieved an unprecedented five-year overall survival above 50%. In metastatic renal cell carcinoma, the same combination has been associated with an overall survival rate exceeding 60% at 3 years in the intention-to-treat population. In the large landscape of ongoing early-phase clinical trials, few novel combinations have achieved a level of efficacy rivaling those new standards of care. What certainly remains to be improved is their safety profiles.

Another area of urgent need is to find novel treatments both for patients who are primary non-responders to ICIs and for those who develop secondary resistance to those therapies. Beyond ICI failure, very few treatments have been studied, and physicians often rely on previously validated standards of care for each specific cancer. Early observational data suggest that exposure to ICIs might modulate the response to standard treatments received after progression. For instance, exceptionally high response rates to chemotherapy have occasionally been documented after ICI failure. Those observations might be secondary to immunotherapy having removed the inhibition initially exerted by tumour cells or other immune cells, followed by cytotoxic chemotherapy-mediated killing of tumour cells. On the other hand, progression-free and the adverse event profiles associated with exposure to targeted therapies (such as BRAF inhibition in melanoma) might be adversely affected by first-line exposure to ICIs.

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