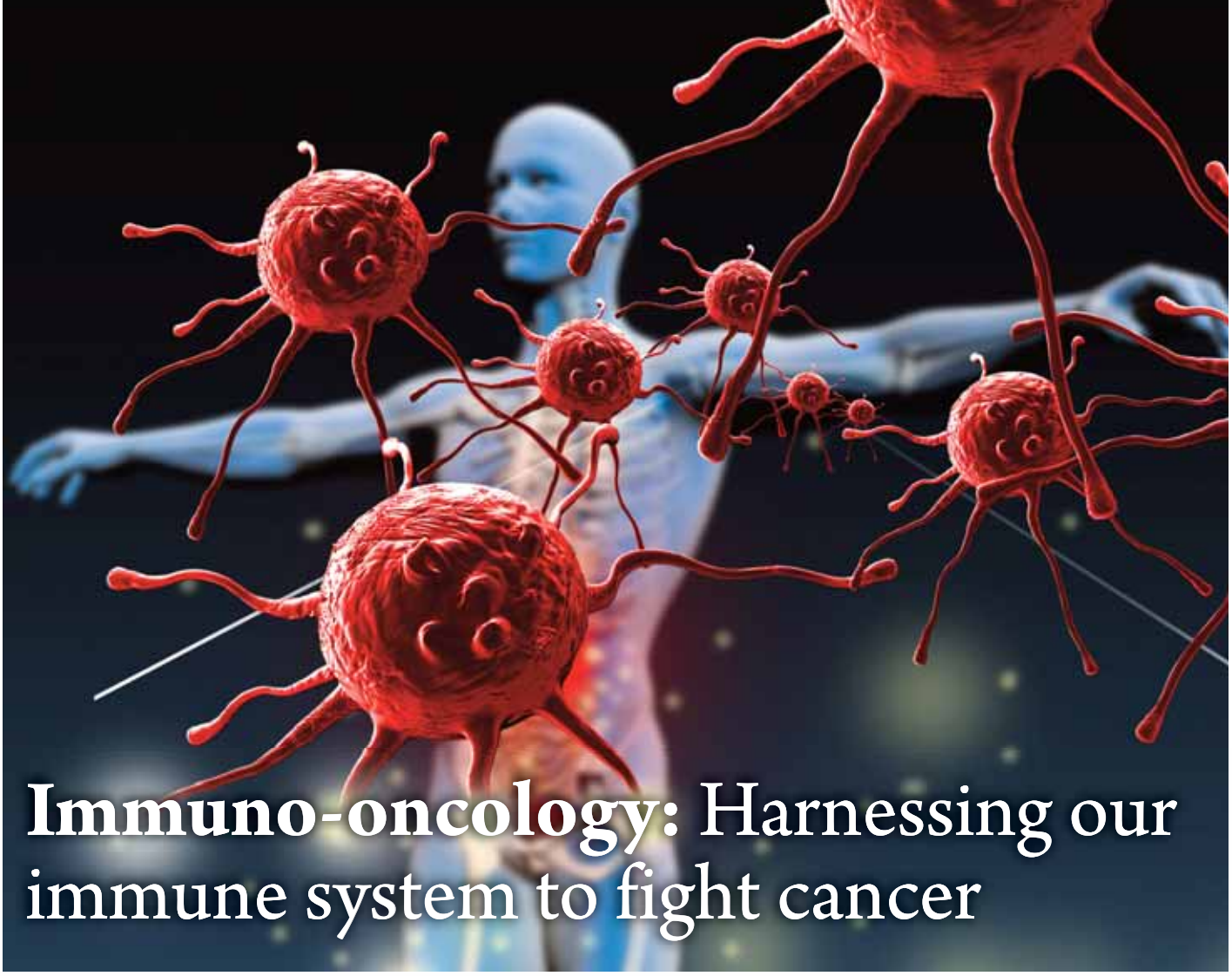

Immuno-oncology: Harnessing our immune system to fight cancer

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Abstract

The history of immunotherapy to treat cancer began in 1891 when the American surgeon William Coley performed intra-tumoural injections with inactivated bacteria in patients with advanced sarcoma, in an attempt to stimulate anti-tumour immunity. Modern immunotherapy gradually made its way over the last 50 years, as a better understanding of anti-cancer immunity has been gained. Immunotherapeutic agents target three essential steps in the immune response to tumour-associated antigens, namely antigen presentation, effector T-cell response, and inhibition of tumour-driven immunosuppression. Conventional chemotherapy and immunotherapy agents differ in their mode of action, predicted endpoints, and toxicities. The development and approval of immunotherapy drugs has therefore challenged our traditional view of conducting clinical trials. Many challenges with great promises still lie ahead, including combination therapies and individualised therapy based on patients' predicted responses to treatments.

Introduction

Cancer immunotherapy began in the late 19th century when the New York surgeon and cancer researcher William Coley noted cases of spontaneous remission of sarcoma in patients who had developed acute *Streptococcus pyogenes* infections.[1,2] Coley hypothesised that *Streptococcus* stimulating the immune system with a bacterial infection might be associated with a bystander anti-tumoural activity that would result in tumour regression. So, in 1891 Coley began treating mainly inoperable sarcoma patients with intra-tumoural injections of initially live and then inactivated *Streptococcus pyogenes* and *Serratia marcescens* (so-called Coley's toxins).[2,3] However Coley's approach fell into disuse, hampered by a cure rate of 10%, an absence of standardised toxin manufacturing, the lack of prospective clinical trials to evaluate the safety and efficacy of this treatment, and the arrival of modern cancer treatments (radiation therapy and chemotherapy).[2,4] One exception is the current use of intravesical injection of live bacillus Calmette-Guérin (BCG) as an efficient approach to treat superficial bladder cancer.[5]

Since Coley's procedure, the concept of immune surveillance has emerged, and it is now well established that the immune system recognises and eliminates cancer cells. A failure in immune surveillance (or immune escape) is associated with cancer initiation and progression.[6,7] Immuno-oncology thus originated as an approach to stimulate or restore the patient's immune response to cancer. Before reviewing the state-of-the-art and future of immunotherapies, it is necessary to describe the processes underlying a protective immunity to cancer and the challenges we face.

Generation and regulation of anti-cancer immunity

Our immune response to tumours follows three main successive steps (Figure 1).[8,9] The initial step, called tumour recognition, occurs when tumour-associated proteins (or antigens) released by dead or dying tumour cells are captured by specific immune cells, mainly dendritic cells. These cells process the antigens and present them on their surface. This is why these dendritic cells are also known as antigen-presenting cells.[10] When dendritic cells process and present tumour-associated antigens, they also need to receive an activation (or maturation) signal, which can occur by a number of different immune-stimulating pathways. Typical immune-stimulating signals, sometimes referred to as "endogenous" adjuvants (in contrast to "exogenous", therapeutically administered adjuvants; see below), are pro-inflammatory cytokines, co-stimulatory CD40/CD40L proteins, factors released by dying tumour cells such as adenosine triphosphate (ATP) or high-mobility group box 1 protein (HMGB1), or toll-like receptor (TLR) ligands.[10]

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The second step involves generating an immune response to the tumour. This occurs when the antigen-presenting dendritic cells travel to the lymph nodes where they elicit an immune response called an antigen-specific T-cell response.[11] If there isn't a co-stimulatory maturation signal, "immature" dendritic cells suppress the immune response to the tumours by promoting the formation of immunosuppressive regulatory T-Cell (T_{reg}), or by inducing T-cell depletion or anergy (the absence of a response to an antigen).[12] This phenomenon of immune suppression is also known as immune tolerance. If the antigen-presenting cell received a co-stimulatory maturation signal, these "matured" dendritic cells provoke or stimulate a T-cell response (mainly effector cytotoxic T cells). This T-cell response is also dependant on specific interactions between dendritic cells and T-cell co-stimulatory molecules.[13,14] For instance, interaction of CD80/CD86 (on dendritic cells) with CD28 (on T cells) or OX40L with OX40 will stimulate, while interaction of CD80/CD86 with CTLA-4 or PD-L1/PD-L2 with PD-1 will suppress T-cell responses (Figure 2). T-cell priming and activation is therefore a critical stage that determines the nature of the immune response.

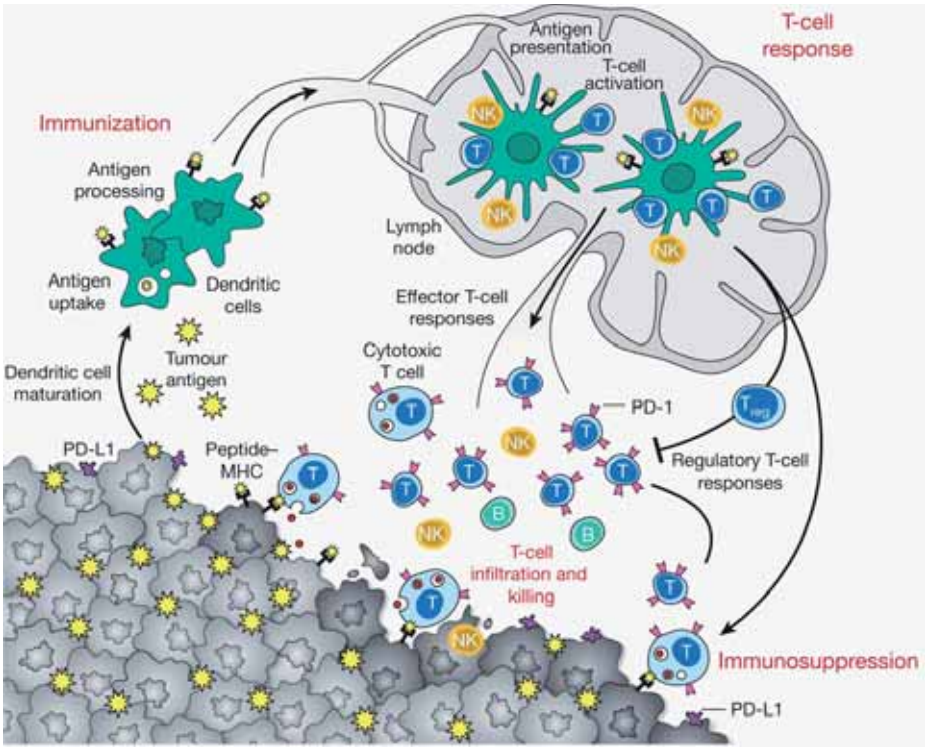

Figure 1. Generation and regulation of anti-tumour immunity

Anti-tumour immunity is initiated with the capture of tumour-associated antigens (delivered by dead or dying tumour cells) by dendritic cells. Tumour antigens are processed and presented on major histocompatibility complex (MHC) molecules to naïve T cells in the lymph node (immunisation). In the presence of a maturation signal ("adjuvant"), and depending on their interaction with T-cell co-stimulatory molecules, dendritic cells elicit an anticancer effector T-cell response (cytotoxic T cell priming and activation). These effector cytotoxic T-cells traffic to and infiltrate the tumour bed, together with B and NK cells, causing the killing of antigen-specific tumour cells. In the absence of a maturation signal in the lymph node, however, dendritic cells induce tolerance by promoting regulatory T-cell (T_{reg}) responses and T-cell anergy. T_{reg} further infiltrate and accumulate into the tumour bed, contributing to the immunosuppressive environment established by tumour cells and other infiltrating myeloid-derived suppressor cells. Notably, tumour cells overexpress the PD-L1 molecule which engages the PD-1 receptor on effector T cells, causing their exhaustion. Immunotherapeutic interventions target the three major steps of anticancer immunity: immunisation, generation of a protective T cell response, and overcoming immunosuppression imposed by the tumour microenvironment. Figure reprinted by permission from Macmillan Publishers Ltd: Nature (volume 480, issue 7378, page 481), copyright (2011).[8]

In the third and last step, cytotoxic T cells exit the lymph node together with other tumour antigen-specific lymphocytes (B cells, natural killer [NK] cells, and natural killer T [NKT] cells), reach the bloodstream, and head toward the tumour site.[8,9] There, they enter the tumour bed where cytotoxic T cells recognise and then kill the cancer cells (Figure 1). In turn, these dead and dying cells provide a novel source of tumour antigens (also called neo-antigens), which initiate a new immunity cycle.[8,9]

However, killing cancer cells is not that simple. Within the tumour site, cytotoxic T cells then face an immunosuppressive environment. Tumour cells, as well as other cells infiltrating the tumour tissue, so-called myeloid-derived suppressor cells (MDSCs), use a variety of strategies to suppress the function of cytotoxic T cells. For instance, tumour cells release T-cell suppressor molecules such as prostaglandin E2 (PGE_2) and indoleamine 2,3-dioxygenase (IDO),[15] while MDSCs produce inhibitory molecules such as arginase and nitric oxide

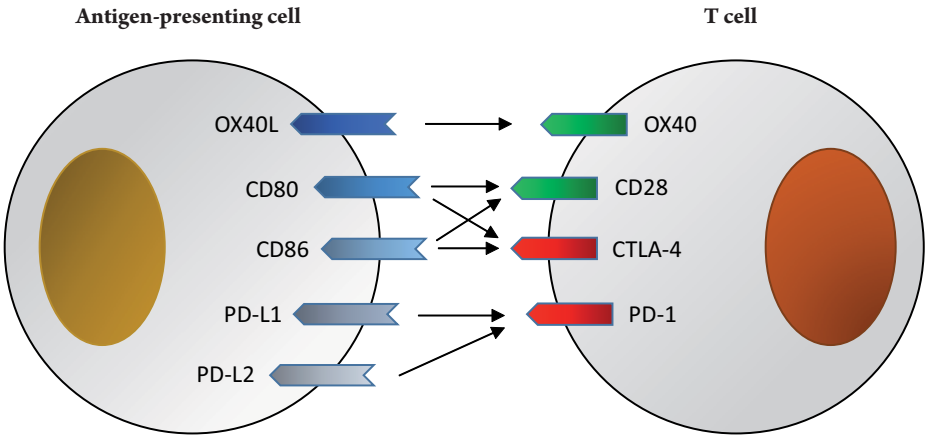

Figure 2. Examples of activating and inhibitory signaling between an antigen-presenting cell and a T cell
The interaction of activating (green) or of inhibitory (red) co-stimulatory molecules on the T cell surface with their respective receptor on the antigen-presenting cell (dendritic cell) contributes to either immune activation and the development of anti-tumour immunity or to immune suppression and the development of immune tolerance, respectively. Of note, tumour cells frequently express programmed cell death ligand (PD-L1/PD-L2) molecules on their surface, which engage PD-1 receptors on cytotoxic T cells, suppressing their anti-tumour activity. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1/PD-L2, programmed cell death protein ligands 1 and 2; OX40L, OX40 ligand; CD, cluster of differentiation (CD28, CD80, and CD86 proteins).

synthase.[16] More importantly, tumour cells express programmed cell death protein ligand (PD-L1/PD-L2) molecules on their surface, which engage PD-1 receptors on the cytotoxic T cells, causing their anergy.[17] Reduced oxygenation within the tumour tissue (intratumoural hypoxia), a common feature of rapidly growing tumours, results in the release of immunosuppressive molecules (e.g., vascular endothelial growth factor A [VEGFA], adenosine, CCL28) that also contribute to the local immunosuppression.[18–21] Alternatively, tumours have also developed mechanisms to interfere with antigen presentation,[8,9] thereby suppressing the initial step of the immune response (Figure 1). All these tumour-driven immunosuppressive mechanisms make it challenging for cytotoxic T cells to efficiently target and kill cancer cells.

Based on our current knowledge of anticancer immunity, described above, immunotherapies can intervene at three critical stages by:

1. stimulating antigen processing and presentation by dendritic cells
2. stimulating the T-cell responses in lymph nodes
3. overcoming the immunosuppressive mechanisms within the tumour microenvironment

Different immunotherapeutic interventions have been proposed at each of these stages. At the first stage, an intervention may be a therapeutic cancer vaccine that introduces tumour-specific antigens from outside of the body (exogenously) to stimulate the T-cell response. At stage 2, an intervention may be delivering adjuvants exogenously that initiate dendritic cell maturation (such as TLR ligands, CD40 antibodies that activate receptors on the dendritic cell, or even by provoking tumour cell lysis and the release of the adjuvant molecules ATP or HMGB1). At stage 3, antagonizing immunosuppression at the tumour site can be attempted by blocking the PD-L1/PD-1 interaction between the tumour cells and the cytotoxic T cells, by counteracting the effect of immunosuppressive molecules (e.g., IDO, adenosine), or by enhancing the recognition of cancer cells by cytotoxic T cells (Figure 3).

Immunotherapies

The aim of anticancer immunotherapy is to initiate, stimulate, or restore anti-tumour immunity without disrupting the self-tolerance mechanisms, which would result in pathological autoimmune inflammatory responses. The better understanding of anticancer immunity acquired over the past 5 decades has allowed a more educated design of immunotherapies, and their use as monotherapy or, more recently, in combination with other treatment regimens (chemotherapy, radiotherapy, and surgery).[4,8]

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In the past, cancer immunotherapies were classified as being either passive or active. Passive immunotherapies were usually defined as those stimulating a patient's own immune response whereas active immunotherapies were those inducing a *de novo* immune response to directly attack tumour cells. However, this definition is often misused in the literature and not always relevant;[22–24] the terms of passive and active therapies can be misleading and should probably be revised. Here, immunotherapies are described according to their ability to either modulate an existing immune response or to provoke a *de novo* or replace a missing immune response (Figure 3 overleaf).

Immunotherapies that modulate the immune response include immunomodulatory monoclonal antibodies (co-stimulatory or blocking antibodies), immunostimulatory cytokines (e.g. interleukin [IL]-2), and small molecules (e.g., inhibitors of immunosuppressive metabolism such as IDO or adenosine inhibitors), which boost the immune response or block immunosuppressive T cell functions (Figure 3).[4,8,9,22,23] Anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) blocking antibodies, also known as checkpoint inhibitors or checkpoint blockers (Figure 3), are FDA-approved immunotherapeutic drugs. They represent a major breakthrough in immuno-oncology. These checkpoint inhibitors can restore anti-tumour T-cell function and showed clinical benefit to some cancer patients (see below).[4,8,9,22,23]

Immunotherapies that provoke a *de novo* or replace a missing immune response include cell therapy (known as adoptive cell transfer), anticancer vaccines, oncolytic viruses, and bispecific T-cell engagers (BiTEs).[4,8,9,22,23] Conventional adoptive cell therapy consists of isolating tumour-infiltrating T cells from a cancer patient; once isolated, the T cells are expanded *in vitro*, and then reintroduced into the patient, providing

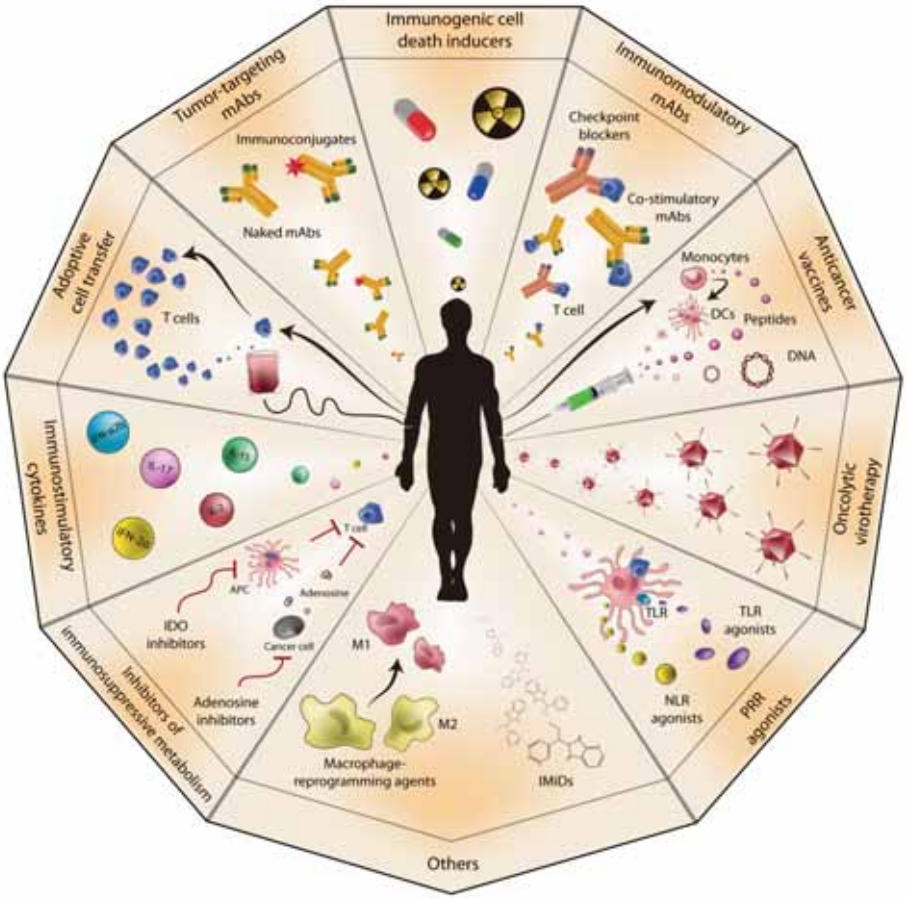

Figure 3. Anticancer immunotherapy

Anti-cancer immunotherapeutics include tumour-targeting (e.g. BiTEs, anti-VEGFA inhibitor) and immunomodulatory (e.g. anti-PD-1 and anti-CTLA-4 immune checkpoint inhibitors) monoclonal antibodies (mAbs); dendritic cell (DC)-, peptide- and DNA-based anticancer vaccines; oncolytic viruses; pattern recognition receptor (PRR) agonists (e.g. TLR agonists); immunostimulatory cytokines (e.g. IL-2); immunogenic cell death inducers (radiation therapy, chemotherapy); inhibitors of immunosuppressive metabolism (e.g. IDO or adenosine inhibitors); and adoptive cell transfer. APC, antigen-presenting cell; IDO, indoleamine 2,3-dioxigenase; IFN, interferon; IL, interleukin; IMiD, immunomodulatory drug; NLR, NOD-like receptor; TLR, Toll-like receptor. Figure reprinted with permission of *Oncotarget*, under the terms of the Creative Commons Attribution License.[23]

immune protective cells. Recently, two very promising cell therapy methods (so-called T cell receptor [TCR] and chimeric antigen receptor [CAR]), which are under development and clinical evaluation, have been described. These promising therapies are based on isolating T cells from a patient's blood; these isolated T cells are then manipulated *in vitro* to redirect their specificity toward tumour-specific antigens, before being reintroduced into the patient. Anticancer vaccines (e.g., dendritic cell-, whole-tumour-, DNA- or peptide-based) deliver tumour-specific antigens to initiate an immune response. Oncolytic viruses (OVs) selectively infect and kill tumour cells. Bispecific T-cell engagers (BiTEs) are antibody-based recombinant molecules that force the recognition of tumour-associated antigens on tumour cells by cytotoxic T cells and the subsequent activation of anti-tumour cytotoxic activity (Figure 3).[4,8,9,22,23]

Clinical study design

Oncology drug development in humans, before marketing approval, has followed a traditional sequence of trials. Phase I trials identify the maximum tolerated dose (MTD) and evaluate the toxicity, pharmacodynamics, and pharmacokinetics of the new drug. In oncology, for ethical reasons, patients and not healthy volunteers are enrolled in phase I trials. Once the MTD has been identified, the recommended phase II dose is established and phase II trials are initiated. Phase II trials assess drug activity and tolerance in usually a few hundred patients. If the new drug shows sufficient activity and reasonable tolerance, phase III studies are initiated. Phase III trials compare the drug to existing treatments or placebo in a larger population.[25]

The recent development of cancer immunotherapies has substantially changed the traditional drug development methodology used in oncology.[26] The development and approval of the immunotherapy pembrolizumab is a good example of how this process has accelerated in recent years.[27] Pembrolizumab is a monoclonal antibody that binds to programmed cell death protein 1 (PD-1) on cytotoxic T cells. This binding prevents programmed cell death ligands 1 and 2 (PD-L1 and PD-L2) proteins, on tumour cells, from interacting with PD-1 that deactivates the cytotoxic T cells and diminishes the immune response. In 2011, a first-in-human phase Ib clinical trial was initiated to identify the recommended phase II dose for patients with advanced solid tumour cancers. However, pembrolizumab seemed to have a high level of activity and so additional patients were enrolled for two other tumour cohorts – melanoma and non-small cell lung cancer (NSCLC). Since oncology trials enrol patients rather than healthy individuals in phase I trials, drug activity can be explored at this early stage. It became increasingly evident that pembrolizumab had superior activity as more patients were assessed, and so additional patients were included in other tumour cohorts. Overall, more than 1,200 patients were recruited in this open-label phase Ib trial. In September 2014, pembrolizumab obtained marketing approval for the treatment of metastatic or inoperable melanoma via an accelerated process based on the phase Ib results. Then in October 2015, this approval was extended to the treatment of those NSCLC patients that express the programmed cell death ligand 1 (PD-L1) protein. This seamless drug development of pembrolizumab was substantially quicker that the traditional sequence of trials.

Although the development time is remarkably shorter, clinical study design with immunotherapies are challenging in other respects. As the tumour response to immunotherapy agents depends on the individual patient's immune function, this response does not follow the same pattern as that observed upon administration of traditional chemotherapy agents. Cytotoxic chemotherapy agents directly attack and kill cancer cells and thus an increase

in dose usually increases the efficacy. However, immune-targeting agents either stimulate immune cells or alternatively prevent cancer cells from deactivating the immune response. With this mechanism of action, dose does not always correlate with efficacy. Furthermore, the anti-tumour response to immunotherapies is often delayed compared to that of conventional cytotoxic therapies. As an example, melanoma patients treated with ipilimumab continued to respond beyond 24 weeks of treatment.[28] In contrast, the tumour response to chemotherapy usually occurs early during treatment.

The use of a traditional phase I study design to evaluate immunotherapies generates issues. First, in many phase I studies, the MTD of the immunotherapeutic agent was never reached. Thus, identifying the minimum effective dose, the maximum effective dose, and the maximum administered dose in phase I immunotherapy studies is more relevant than the MTD for estimating the recommended phase II dose.[29] Furthermore, the sample size of expansion cohorts in phase I immunotherapy studies are often not justified, despite having efficacy as exploratory objectives. When designing these trials, it is important to ensure that they are designed with the same statistical rigour as traditional phase II studies – allowing for false-positive and false-negative results and with interim futility stopping rules to prevent unethical treatment of patients.

At present, the Response Criteria In Solid Tumours (RECIST) classification is used to assess tumour response required to evaluate new treatments in oncology. However, with immunotherapies there is often an initial tumour flaring, an increase in tumour size possibly in response to inflammation, before eventual shrinkage. Using RECIST v1.1, an increase of at least 20% in the sum of the tumour lesion diameters would be classified as disease progression.[30,31] With treatments other than immunotherapies, this would result in a modification of treatment strategy. However, in the case of immunotherapies, this type of pseudo-progression may be a clear indication of a treatment response. Thus, RECIST, which assesses tumour response for outcomes such as progression-free survival (PFS), objective response rate (ORR) etc., needs to be adapted for immunotherapy trials. There have been a number of attempts to establish new classifications, e.g., iRECIST,[32,33] irRECIST,[32,33] and immune-related response criteria (irRC),[34,35] but these need validation and consensus.

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Currently, most immunotherapy trials continue to use the RECIST classification to evaluate the tumour response for the primary endpoints (such as PFS, ORR). These traditional endpoints are considered acceptable for regulatory approval. In addition, some of these endpoints have been correlated with overall survival and considered as surrogate endpoints. However, to investigate immunotherapy-specific endpoints, such as immune-related PFS (irPFS) assessed by immunotherapy-specific classification (such as iRECIST, irRECIST, and irRC), these endpoints are often included as secondary endpoints. In addition, a central review of the imagery used to assess response is also often included. The aim is now to evaluate these new classifications for assessment of tumour response, as well as to validate these endpoints as surrogate endpoints for overall survival.

As with efficacy, the toxicity observed with immunotherapies does not follow the same pattern as that observed with traditional chemotherapy agents. Furthermore, immunotherapies have different toxicity profiles compared to cytotoxic agents. The toxicity profile depends on the immunotherapy agent, its mode of action, and the type of tumour that it targets.[36] The toxicities observed can broadly be divided into infusion reactions and immune-related adverse events (irAEs).[37] Infusional reactions, allergic or non-allergic, are immune reactions that most frequently occur during the first administration of treatment.[38,39] Immunotherapies in general have a low incidence of infusion reactions. However, some immunotherapies have a non-negligible incidence of non-allergic reactions resulting from cytokine release. The release of cytokines causes a variety of symptoms, including fever, nausea, chills, hypotension, tachycardia, and fatigue. In terms of irAEs, the most frequently affected organs are the skin, colon, endocrine organs, liver, and lungs. Accordingly, the most common irAEs are diarrhoea, rashes, and fatigue.[40] In contrast to chemotherapies, the onset of irAEs is often delayed, some beginning as long as 1 year after treatment. Overall, immunotherapeutics are well tolerated but severe and life-threatening toxicities do occur. Clinical trial design should allow for the long-term collection of toxicity data and the possible relatedness to the immunotherapy. This is achievable in most cancer studies because extended patients' follow-up is usually incorporated to evaluate the overall survival benefit.

Patient selection is vital in immunotherapy studies. Despite the high activity of immunotherapies, like pembrolizumab and nivolumab, in treating certain cancers, only a minority of patients have long lasting remissions. Considering the toxicity profile, careful identification and selection of patients expected to benefit from immunotherapies has become essential. Patients with a pre-existing immune response and more inflamed tumours tend to respond better.[41]

The fact that patients with a pre-existing immune response tend to respond better to immunotherapies also provides a rationale for combining immunotherapies with other more classical therapies, including chemotherapies, radiotherapies etc. These classical therapies kill tumour cells liberating antigens that prime the immune system. In addition, radiotherapy induces an abscopal effect, the occurrence of an immune response outside of the irradiated field. Furthermore, combining immunotherapeutic agents targeting distinct steps of the immune response and at different time points might also prove to be beneficial.[4,8]

> Our increase in knowledge of how the immune system responds to cancer and the development of immunotherapies that target these different stages have introduced new weapons in the arsenal to fight cancer. This development has also challenged the traditional way to develop and approve new drugs.

In summary, immuno-oncology is only in its infancy. Our increase in knowledge of how the immune system responds to cancer and the development of immunotherapies

that target these different stages have introduced new weapons in the arsenal to fight cancer. This development has also challenged the traditional way to develop and approve new drugs. Despite the proven efficacy of immunotherapies, these treatments are only effective for certain patients. There remain a number of important issues that need to be addressed, including: Which patients will benefit most from treatment and how should we combine immunotherapeutics with traditional therapies?

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Conflicts of interest

The authors declare no conflicts of interest related to this article.

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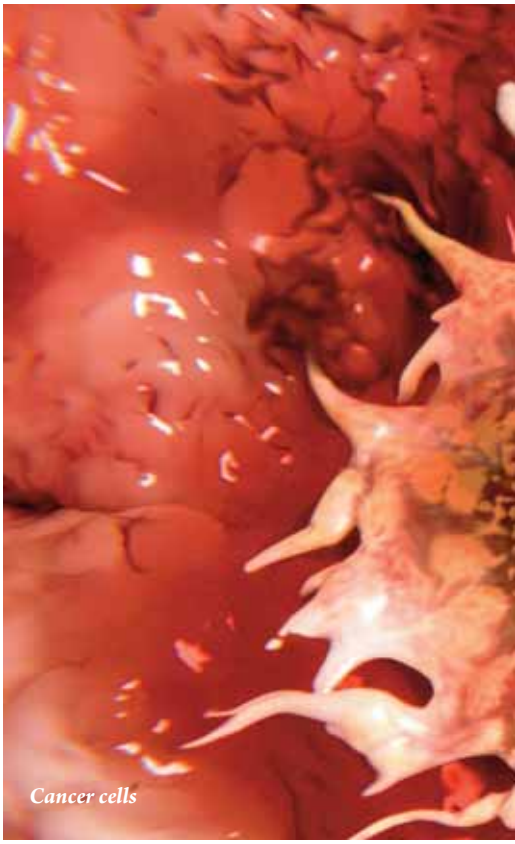

Cancer cells

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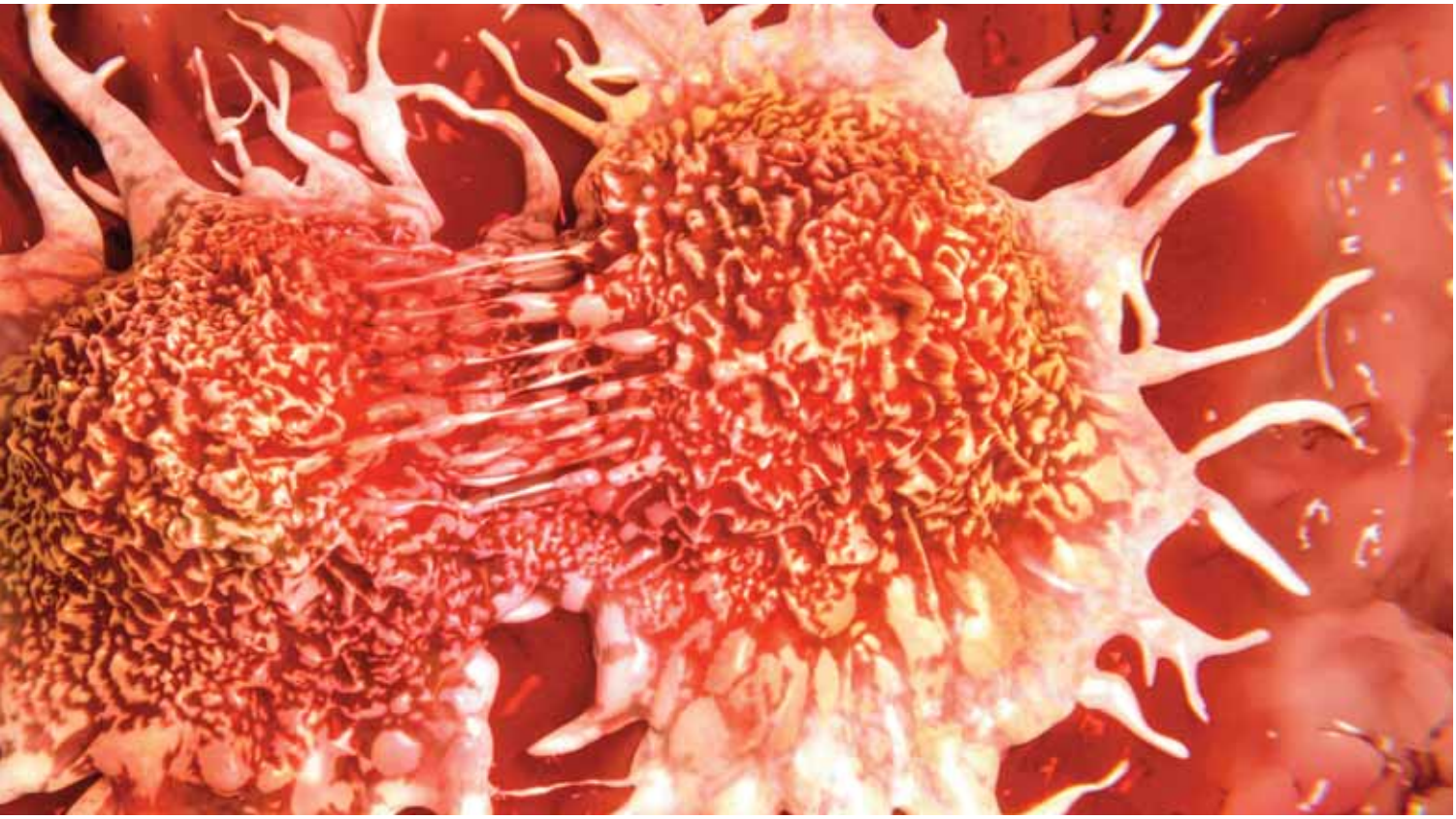

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