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Review

Second- and third-generation drugs for immuno-oncology treatment—The more the better?

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Abstract Recent success in cancer immunotherapy (anti-CTLA-4, anti-PD1/PD-L1) has confirmed the hypothesis that the immune system can control many cancers across various histologies, in some cases producing durable responses in a way not seen with many small-molecule drugs. However, only less than 25% of all patients do respond to immuno-oncology drugs and several resistance mechanisms have been identified (e.g. T-cell exhaustion, overexpression of caspase-8 and β-catenin, PD-1/PD-L1 gene amplification, MHC-I/II mutations). To improve response rates and to overcome resistance, novel second- and third-generation immuno-oncology drugs are currently evaluated in ongoing phase I/II trials (either alone or in combination) including novel inhibitory compounds (e.g. TIM-3, VISTA, LAG-3, IDO, KIR) and newly developed co-stimulatory antibodies (e.g. CD40, GITR, OX40, CD137, ICOS). It is important to note that co-stimulatory agents strikingly differ in their proposed mechanism of action compared with monoclonal antibodies that accomplish immune activation by blocking negative checkpoint molecules such as CTLA-4 or PD-1/PD-1 or others. Indeed, the prospect of combining agonistic with antagonistic agents is enticing and represents a real immunologic opportunity to 'step on the gas' while 'cutting the brakes', although this strategy as a novel cancer therapy has not been universally endorsed so far. Concerns include the prospect of triggering cytokine-release syndromes, autoimmune reactions and hyper immune stimulation leading to activation-induced cell death or tolerance, however, toxicity

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has not been a major issue in the clinical trials reported so far. Although initial phase I/II clinical trials of agonistic and novel antagonistic drugs have shown highly promising results in the absence of disabling toxicity, both in single-agent studies and in combination with chemotherapy or other immune system targeting drugs; however, numerous questions remain about dose, schedule, route of administration and formulation as well as identifying the appropriate patient populations. In our view, with such a wealth of potential mechanisms of action and with the ability to fine-tune monoclonal antibody structure and function to suit particular requirements, the second and third wave of immuno-oncology drugs are likely to provide rapid advances with new combinations of novel immunotherapy (especially co-stimulatory antibodies). Here, we will review the mechanisms of action and the clinical data of these new antibodies and discuss the major issues facing this rapidly evolving field.

1. Introduction

In recent decades, systemic treatment options for patients with different types of cancers have evolved from chemotherapy through targeted-therapies to the more recent immuno-oncology agents, and emerging evidence on the role of the anti-tumour activity of the immune system has generated great interest in immunotherapy even for tumours that were historically considered as non-immunogenic [1].

Immuno-oncology is a novel therapeutic strategy currently being evaluated for many malignancies. This approach differs from traditional modalities, which target the tumour directly or aim to disrupt the tumour blood supply, as it is designed to potentiate the patient's immune response to tumour cells. Immunotherapy is now emerging as a major modality in cancer treatment focussing on development of inhibitors or co-stimulatory agents of the cellular mediators of cancer-induced immunosuppression (immune checkpoints) to boost anti-tumour immune responses. Different immunologic approaches targeting immune checkpoint pathways are showing promise in development, and preclinical and clinical evidence provides the rationale for investigating the combination of co-stimulatory and inhibitory monoclonal antibodies to establish a novel or re-instating a pre-existing anti-tumour immune response.

The immune system is capable of identifying tumour-associated antigens (so-called neo-antigens) and eliminating the tumour cells expressing them. Expression of these neo-antigens (new epitopes) is regarded to be a consequence of new mutations (e.g. EGFR and/or DNA damage) [1]. Immune checkpoints refer to multiple inhibitory and co-stimulatory pathways that counteract certain crucial steps of T-cell-mediated immunity to maintain self-tolerance and modulate the duration and amplitude of immune responses.

Recently, the understanding of several checkpoints that shut down the immune system as an immunosuppressive mechanism in tumours has evoked a paradigm shift in cancer treatment [2]. Immune checkpoints are initiated primarily through T cell inhibiting and stimulating receptors and their ligands, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4, CD152), PD-1 (programmed cell death-1, CD279) and PD-L1 (CD274) or PD-L2 (CD273; programmed cell death ligand-1, -2), among many others (reviewed by Refs. [3,4]).

Understanding how the immune system affects cancer development and progression has been one of the most challenging questions in immunology. It is now generally accepted that the immune system plays a dual role in cancer: it cannot only suppress tumour growth by destroying cancer cells or inhibiting their out-growth but also promote tumour progression either by selecting for tumour cells that are more fit to survive in an immunocompetent patient or by establishing conditions within the tumour microenvironment that facilitate tumour out-growth ('cancer immune-editing') [5].

To improve response rates following immune therapy and to overcome resistance, novel second- and third-generation immuno-oncology drugs are currently evaluated in ongoing phase I–III trials (either alone or in combination) including novel inhibitory compounds (e.g. TIM-3, VISTA, LAG-3, IDO, KIR) and newly developed co-stimulatory antibodies (e.g. CD40, GITR, OX40, CD137, ICOS). Here, we will review the mechanisms of action and the clinical data of these new molecules and discuss the major issues facing this rapidly evolving field.

2. Immune cells in defence against tumours

The most essential role of the immune system in humans is to eradicate invading pathogens by inducing a protective immunity and not to jeopardise the host by inducing tolerance to self-tissues. This is achieved through a fine tuning of antigen-presenting cells, T cell, B cells and NK cell activities (in concert with the B7 protein family) in initiation, differentiation, the effector phase and termination of the immune response [6].