EDITORIAL

Immune-checkpoint blockade: the springboard for immuno-combination therapy

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Today, it is well accepted that the immune system plays a role in both tumour destruction and tumour promotion. A clinically apparent tumour is one that, even under the pressure of the immune system, has escaped from immune recognition. With the more recent discovery of the mechanisms of tumour escape from the immune system, immunotherapy has taken over the driver's seat in targeted and personalized cancer therapy. Cancer immunotherapy has become a more attractive therapeutic option compared to traditional chemotherapy, radiation and even targeted therapy, mostly due to the latter's lack of specificity for cancer cells and/or high propensity for resistance. Furthermore, immunotherapy holds the greatest potential to destroy tumours with minimal side effects to normal tissues, and to prevent recurrence through the development of long-term memory.¹ In addition, the plethora of somatic mutations and their continuous evolution in cancer create challenges for targeted therapies, whereas new antigens are exposed to immune recognition. However, transformed cells dampen the host immune response by limiting their display of neo-antigens and paralyzing infiltrating immune effector functions.² That said, efforts to boost the immune system with various vaccine strategies, cytokine regimens and adoptive T-cell therapy have clouded an underlying issue in cancer—negative regulation of the immune system. The field of cancer immunotherapy took a turn for the better when immune-enhancing or 'stepping on the gas pedal' efforts moved towards reprogramming effector functions and relieving immune suppression, often referred as 'taking off the brakes'. This led to the development of the clinically successful agent ipilimumab (Yervoy; Bristol-Myers Squibb, New York City, NY, USA), an anti-cytotoxic T-lymphocyte-associate protein (CTLA)-4 humanized antibody that was approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of metastatic melanoma.³

Immune checkpoints normally function to control excessive immune activation and may also be a means of control by tumours. Immune checkpoint blockade agents such as ipilimumab target molecules are involved in the regulation of T-cells rather than targeting malignant cells directly, such as with targeted drugs. For that reason, their astonishing clinical success was not foreseen. Moreover, the end result of immune checkpoint blockade is not to attack a target on a tumour cell, but rather to remove natural inhibitory responses that are impeding an effective antitumour response.⁴ Preclinical studies demonstrated that the complete loss of CTLA-4 led to massive lymphoproliferation, autoimmunity and death in mice⁵ and partial inhibition with a monoclonal antibody demonstrated that a therapeutic window could be achieved.⁶ Following clinical trials with anti-CTLA-4 agents, the discovery of inhibiting the checkpoint protein programmed death receptor (PD)-1 led to a more specific activation of T-lymphocytes in the periphery. Furthermore, the discovery of its ligands, PD-L1 and PD-L2, on tumour tissues was the precursor to the development of anti-PD-1 monoclonal antibodies such as nivolumab, but also anti-PD-L1 agents such as MPDL3280A. As was expected because of the expression of the PD-1 receptor on activated T-cells, and the expression of PD-L1 on

malignant cells, these agents achieve higher response rates and are accompanied by less toxicities.

Large-scale clinical trials have demonstrated that immune checkpoint blockade treatment leads to robust, durable clinical responses in patients with advanced malignancies with some life-threatening, but mostly manageable toxicities. To date, three immune checkpoint agents have been approved by the FDA: ipilimumab, nivolumab and pembrolizumab, for the treatment of metastatic melanoma. Anti-immune checkpoint therapy will not be limited to the treatment of melanoma, but high expectations are also in place for the treatment of lung cancer, renal cancer, bladder cancer, lymphoma and other cancer types. It is thought that the negative regulation of T-lymphocytes may account for the unsuccessful vaccine and other immune-boosting strategies in the past. Today, sipuleucel-T still stands alone as the only therapeutic vaccine licensed for the treatment of cancer,⁷ and it is becoming clearer as to why.

Identifying responders from non-responders in immunotherapy has always presented a challenge. While targeted therapies target a specific genotype, immune checkpoint blockade targets molecules involved in the regulation of T-cells; therefore, identifying patients who would respond to this treatment is problematic. To date, the most useful biomarker has been PD-L1, yet its expression levels are still not quite accurate enough; patients with low or no expression of PD-L1 do not respond to anti-PD-1 or anti-PD-L1 therapy, while not all patients with high PD-L1 expression levels are responders. Of note, PD-L1 can only provide predictive and prognostic value for anti-PD-1 or anti-PD-L1 agents, and not anti-CTLA-4 agents. Moreover, anti-immune checkpoint antibodies unleash dynamic and complex responses whereby the tumour microenvironment influences PD-L1 expression.⁴ Therefore, the complexity of the regulation of checkpoint receptors and their ligands makes it difficult to rely on one immunologic biomarker to select patients for treatment.⁴ The inconsistent response rates remain an issue and may be due in part to advanced disease and the immunosuppressive effects of the tumour. However, this challenge has catalysed the idea that was long-coming, immuno-combination therapy.

The main goal of immunotherapy is to create a tumour microenvironment in which multiple arms of the immune system can effectively attack and destroy the malignancy. This is where combination therapy is needed to simultaneously increase antigen load, relieve immune suppression and prompt the infiltration of immune cells to the tumour. Conventional cytotoxic agents and targeted therapies both modulate immune responses, and therefore can be effectively used in combination with immunotherapies to improve clinical outcomes.⁸ This can be achieved through the direct killing of the tumour, attenuation of suppressive immune cells or by augmenting tumour antigen presentation by dendritic cells (DCs). In fact, with immunotherapy, it is very unlikely that a monotherapy can generate a robust and sustainable antitumour immune response for it usually targets an individual component of the antitumour response, especially in a case of a non-immunogenic tumour such as pancreatic ductal adenocarcinoma.^{4,8} A combinatory approach allows therapies to work synergistically and also has the potential to benefit a broader patient population.⁹

Tumours downregulate their antigenicity through various mechanisms in response to selective pressure by the immune system. As a result, immunological tolerance must be destroyed to allow tumour antigen-specific cytotoxic T-cell responses. Tumour-targeted oncolytic viruses (TOVs) can selectively infect and replicate within the tumour cells, exposing tumour-associated antigens and disrupting the immunotolerance employed by the tumour while re-engaging adaptive immune effector responses. Combining an agent that can cause disruption to the tumour microenvironment, such as a TOV, with an immunomodulating agent, such as anti-CTLA-4 or anti-PD-1 antibodies, can maximize immune-stimulating and immune-recruiting inflammatory responses.² TOVs induce T-cell infiltration to the tumour bed, while immune checkpoint inhibitors alleviate immunosuppression. TOVs in combination with immune checkpoint inhibitors can therefore potentiate and activate the immune system synergistically, ultimately creating a pro-inflammatory environment.

Ipilimumab or pembrolizumab in combination with talimogene laherparepvec (T-VEC), an engineered herpes simplex virus-1, is currently in early clinical testing in patients with unresected melanoma (clinicaltrials.org: NCT01740297 and NCT02263508, respectively). The approval of T-VEC will mark the first TOV to be approved as a cancer therapeutic outside of China. The compatibility of TOVs and other immunotherapies will most likely encourage the adoption of oncolytic agents as both monotherapies and in combination strategies with immune checkpoint antibodies.¹⁰ Early results have demonstrated that there are no added toxicities in the T-VEC+ipilimumab arm compared with ipilimumab alone. These results are very encouraging, especially for the field of oncolytic immunotherapy.

Owing to the quick success of immune checkpoint-blocking agents, immunotherapy is now back in the running in cancer treatment. The future is looking bright for combining more than one immunotherapy, with immune checkpoint antibodies being the common denominator. Understanding the mechanism and effect of one therapy will allow the determination of a second therapy with a synergistic effect. Future studies must then determine the appropriate timing, dosing and sequence schedule of the two (or more) therapies. Accurate biomarkers are still lacking for both predicting patients' suitability for treatment as well for prognostic and monitoring applications. Combining immune checkpoint antibodies with other immune-stimulating

agents such as conventional drugs, targeted agents and, most promisingly, TOVs may increase the tumour types and individual patient profiles in which a durable clinical benefit can be achieved. TOVs are finally being recognized for their ability to stimulate antitumour immunity, and, with anti-CTLA-4 and anti-PD-1 agents on the market, TOVs may finally have met their perfect match. It has never been a more promising era for cancer immunotherapy and personalized medicine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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