Perspective

Program death-1 (PD-1) receptor pathway inhibition in cancer medicine: a perspective on clinical efficacy and associated toxicities

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Abstract: Enlisting the host's immune system to destroy and eradicate tumors in patients with advanced cancer has long been pursued by researchers and clinicians worldwide. The development of immune checkpoint inhibitors—agents targeting co-stimulatory T cell receptors or their ligands—have demonstrated substantial and durable anti-tumor activity in selected patients with different tumor types, renewed our enthusiasm for immunotherapy, and generated large research efforts, establishing Immuno-Oncology as a solid discipline of cancer medicine. The first immune checkpoint inhibitor, ipilimumab—a cytotoxic T lymphocyte associated antigen-4 (CTLA-4) inhibitor received FDA approval for patients with melanoma in different stages of disease. PD-1 inhibitors have better efficacy and safety profile than their predecessor. Several agents inhibiting this pathway have completed early stages of drug development (biology, pharmacokinetics, safety, efficacy, etc.) and are rapidly finding their way to the clinic. Of these, three already received FDA approval for different indications: Nivolumab (Bristol Myers Squibb), Pembrolizumab (Merck & Co), and Alemtuzumab (Genentech). As expected, their toxicity profile predominantly includes immune related adverse events. The majority of these adverse events are manageable and grade 3/4 toxicities are only observed in 1–3% of patients. Other aspects of clinical interest include: (I) while toxicities are consistent among different agents, their incidence vary slightly among different tumor types; (II) stabilization of tumor growth is observed in a large number of patients; however, objective responses are still reserved to a minority; (III) PD-L1 expression on tumor cells is the most predictive biomarker. Nonetheless, a considerable number of PD-L1(–) patients experience objective responses and differences in survival according to PD-L1 status are not uniform; and (IV) when compared with cytotoxic chemotherapy and other targeted therapies, the duration of responses and safety profile seem to be major advantages among responders to this group of novel biologicals.

Keywords: Cancer immunotherapy; immunological tolerance; program death-1 receptor (PD-1 receptor)

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Cancer immunotherapy

Inducing specific recognition and destruction of tumors by the host's immune system has been a promising but elusive treatment strategy for several decades. Historical observations of striking immune mediated anti-tumor responses among cancer patients have stimulated substantial research efforts aimed at identifying the factors involved in these processes. Clinical observations of patients who attained substantial tumor responses after episodes of systemic infections caused by Streptococcus pyogenes, led Dr. Coley to design a series of experiments injecting streptococcal cultures to patients with sarcoma to

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evaluate the potential to induce immune cross-reactivity and eradication of tumor cells (1,2). Subsequent efforts culminated with the approval of intracavitary administration of Bacillus Calmette-Guerin (BCG) to treat patients with superficial non-muscle invasive urothelial carcinomas of ther bladder (3), interferon for several tumor types (4-6), and interleukin-2 for melanoma and renal cell carcinoma (7,8), among others.

Immunological tolerance

Normal individuals are tolerant to their own antigens and discriminate against foreign antigens. During the maturation process in lymphoid organs—usually before birth, all lymphocytes undergo a phase, in which antigen exposure results in tolerance instead of activation. Clones of lymphocytes that become active when exposed to self-antigens are suppressed to avoid responses against self-antigens. This process is known as central tolerance. Alternatively, peripheral tolerance is induced by the recognition of antigens without adequate levels of co-stimulators—which are necessary for the activation of lymphocytes or by the repeated and persistent stimulation by self-antigens in peripheral tissues.

The term immunological tolerance was first described by Sir Frank Burnet in 1949 and later confirmed by Billingham, Brent, and Medawar in 1953 through experiments with different strains of *CBA* and *A* strain mice and Rhode Island Red and White Leghorn chicken (9). In these experiments, the investigators, demonstrated: (I) that immunological tolerance develops in utero. Mice and chicken never or very limitedly develop strong immunological reactions against foreign antigens inoculated in utero. These animals become tolerant to the inoculated tissue and to re-exposure to the same antigen in their adult life; (II) acquired immunological tolerance is highly specific: The inoculated animals maintained their tolerance for the originally exposed antigens, while rejecting other foreign tissues; (III) acquired immunological tolerance is due to a host's specific acceptance of foreign antigens rather than a modification in the inoculated tissues. These pivotal discoveries made Sirs Medawar and Burnet the recipients of the Nobel prize of Medicine in 1960 and served as cornerstone for the development of organ transplantation and modern immunological therapies (10). Moreover, the role of immunological tolerance in the etiology of cancer became widely recognized (11).

"Programmed death-1" (PD-1) receptor and its ligands

PD-1 (CD279) is an Immunoglobulin superfamily member expressed in a subpopulation of CD4– CD8– normal thymocytes and induced in peripheral lymphocytes following activation. Ishida, Honjo and others discovered the receptor searching for genes associated with programmed cell death, or apoptosis in 1992 (12). Subsequently, Nishimura and colleagues developed the PD-1 knockout mouse model (13). These mice grow normally but develop moderate splenomegaly. Unlike the CTLA-4 knockout mouse model, the PD-1 knockout mouse survives (14). Their proliferative B cell response is augmented along with increased serum levels of certain immunoglobulins (13). PD-1 deficient mice also develop a number of autoimmune diseases, suggesting the very important role of this receptor in immunologic tolerance through negative regulation of proliferation and differentiation of B cells. Multiple subsequent studies confirmed the importance of the B7-H1/CD80 pathway in the induction and maintenance of tolerance in T cells (15).

Characteristics of PD-1 and PD-L1

The PD-1 protein is a co-inhibitor receptor of T cells with a similar structure to that of CTLA-4 but with different biologic function and specificity for ligands. PD-1 has two known ligands: PD-L1 (B7-H1 or CD274) and PD-L2 (B7-DC or CD273). There is greater affinity for PD-L1. Unlike the ligands of CTLA-4 CD80 (B7-1) and CD86 (B7-2), PD-L1 is selectively expressed and inducible in lymphoid, and non-lymphoid tissues; in different tumors (16) and in other cells of the tumor microenvironment, in response to inflammatory stimuli (17). The expression of PD-L2 is more limited (18). Latchman and colleagues described PD-L2, a second ligand for PD-1 and proved that inhibition of PD-L2, substantially inhibits T cell receptor (TCR)-mediated proliferation and cytokine production by CD4+ T cells. These researchers also demonstrated redundancy in the activity of these two receptors (19). The PD-1/PD-L1 pathway can be used by tumor cells for their own protection from immunological responses mediated by T cells (20,21). In fact, an increased regulation of PD-L1 is associated with decreased immunological activation and adverse clinical results. The increased regulation of PD-L1 in tumor cells can inhibit the production of cytokines and cytolytic activity of PD-1(+) and tumor-infiltrating T cells with CD4(+) and CD8(+) surface

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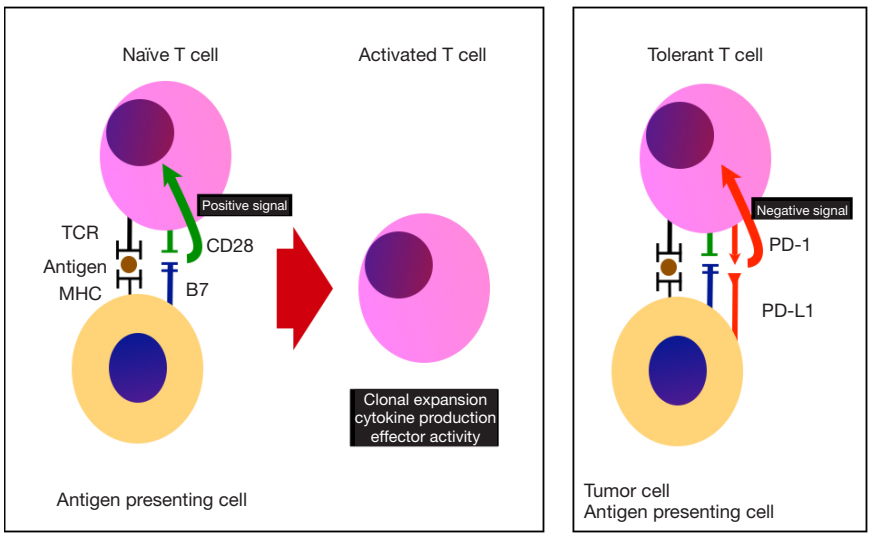

Figure 1 Stimulatory and inhibitory signals in T cell activation. Naïve T lymphocytes are introduced to an antigen by an antigen-presenting cell. This interaction occurs through the binding of the T cell receptor (lymphocyte surface) and the receptor of the major histocompatibility complex (MHC) (surface of the antigen presenting cell). The second step takes place through the binding of CD28 and its ligand B7 (CD80/86). Once this interaction occurs, the cell learns the characteristics of the antigen, secretes cytokines, clonally expands, and performs effector functions. The right panel depicts the interaction of PD1 and PD-L1 with a resulting negative signal, and T-cell inactivation. The inhibitor antibodies of PD-1, PD-L1, or PD-L2 block the contact of these two receptors, inhibit the negative signal, and reactivate T cells.

expression. Hence, the inhibition of PD1 and PD-L1 is known to enhance the immune responses *in vitro* and mediate anti-tumor activity in animals (22) and humans (*Figure 1*).

Expression of PD-L1 in human malignancies

The immunohistochemistry expression of PD-L1 by cancer cells varies substantially (23). PD-L1 is overexpressed on the surface of non-small cell lung cancer (NSCLC) cells between 21–95%; melanoma 38–100%; kidney cancer 14–44%; bladder 20–28%; head and neck 31–66%; breast 18–50%; thymic carcinoma 88-100%; multiple myeloma 93% (23). Several groups of investigators have reported worse clinical outcomes among a variety of patients with PD-L1(+) expressing malignancies (24-28). Recently, Zhang and others reported a meta-analysis confirming an adverse prognosis associated with the expression of PD-L1 on tumor cells and PD-1 on tumor-infiltrating lymphocytes (TIL) by immunohistochemistry in patients with epithelial-originating malignancies (29). The investigators found a significantly poorer survival among patients with PD-L1(+) epithelial malignancies compared with those with PD-L1(–) tumor tissues (HR 1.81; 95% CI, 1.33–2.46; P<0.001). Similarly, patients with PD-1(+) TILs had significantly shorter overall survival than the PD-1(–) group (HR 2.53; 95% CI, 1.22–5.21; P=0.012). Furthermore, all subgroups with PD-L1(+) tumors showed consistent trends toward unfavorable prognoses regardless of the assay utilized for the evaluation of PD-L1. The expression of PD-L1 has also been studied in hematological malignancies including Hodgkin's disease, non-Hodgkin's lymphomas, and multiple myeloma (30-33). In classic Hodgkin's lymphoma, alterations in chromosome 9p24.1 increase the abundance of the PD-1 ligands, PD-L1 and PDL2, and promote their induction through Janus kinase (JAK) signal transducer and activator of transcription (STAT) signaling. Early responses in patients with Hodgkin's disease led to a clinical trial for patients with relapsed or refractory disease (ClinicalTrials.gov number, NCT01592370). Twenty of 23 patients attained objective responses (4 complete responses and 16 partial responses). The rate of progression-free survival at 24 weeks was 86% (95% CI, 62% to 95%). The median survival for responders had not been reached after 40 weeks of follow-up (34).

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Table 1 PD-1 pathway agents under development

Target	Agent	Structure	Manufacturer	Indication
PD-1	Nivolumab	Human IgG4 kappa	Bristol-Myers Squibb; Ono pharmaceutical, Co.	Melanoma; NSCLC; head & neck
	Pembrolizumab	Humanized IgG4	Merck & Co.	Melanoma; NSCLC
	Pidilizumab	Humanized IgG1	CureTech Ltd	DLBCL; melanoma
	AMP-514	Humanized IgG4	MedImmune	Advanced malignancies
	AUNP-12	Peptide Agonist	Aurigene Pierre Fabre	Advanced malignancies
PD-L1	BMS-936559	Human IgG4	Bristol-Myers Squibb	Advanced malignancies
	Atezolizumab	Human IgG1	Genentech & Roche	Bladder; NSCLC
	Durvalumab	Humanized IgG1	Astra Zeneca	Glioblastoma; head and neck; NSCLC; colorectal; bladder
	Avelumab	Fully Humanized IgG1	Merck KGaA EMD Serono, Pfizer	Advanced malignancies; NSCLC
PD-L2	AMP-224	PD-L2 IgG2a fusion protein	Amplimmune	Advanced malignancies

Modified and adapted with permission from Ma *et al*. (35). PD-1, programmed death-1; NSCLC, non-small cell lung cancer; DLBCL, diffuse large B cell lymphoma.

PD1 and PD-L1 inhibition as cancer therapies

Ten monoclonal antibodies with high affinity for PD-1 or its ligands are under development (*Table 1*). Extensive basic and clinical research has demonstrated important signals of anti-tumor activity in several tumor types. As of July 2016, this group of agents has received approval in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma (nivolumab) or unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (pembrolizumab) (36-41), metastatic squamous NSCLC with progression on or after platinum-based chemotherapy (nivolumab) (42,43), or metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy (pembrolizumab) (44), advanced renal cell carcinoma (nivolumab), in patients who have received prior anti-angiogenic therapy (45,46), locally advanced or metastatic urothelial carcinoma (atezolizumab) who have experienced disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (47), and patients with Hodgkin's disease (nivolumab) that have relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation treatment with brentuximab vedotin (Adcetris) (34). Approval for recurrent head and neck carcinoma is expected before the end of 2016 and submissions for other indications are underway. While a major advance in cancer medicine, treatment with this group of agents is associated with major objective responses in a limited group of patients—similar to traditional cytotoxics; and much like chemotherapy, the combination of these agents result in greater toxicity (38). Nonetheless, in contrast with traditional cytotoxic chemotherapy, the responses induced by checkpoint inhibitors can be long lasting, and occasionally, major anti-tumor responses may follow long-term stabilization of tumor growth (48).

Biological markers

The U. S. Food and Drug Administration approved 18 new cancer agents in 2015, and most of them corresponded to targeted therapies. Predictive biomarkers for these therapies are aimed at selecting subgroups of patients with the greatest likelihood of benefit while sparing others from unnecessary expenditures and toxicities. Hence, the development of specific biomarkers concomitantly with these agents has become more important than ever before (49). Ascertaining biological markers for immune modulating therapies are particularly challenging due to our limited knowledge of the immune system and its dynamic

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interactions with the microenvironment and other cellular structures. These limitations have led to a lack of uniform standardization, quantification, and interpretation of predictive biomarkers in immunology (50).

As previously discussed, while PD-L1 is widely expressed among different tumor tissues, PD-L2 is more often restricted to immune cells. Therefore, the immunohistochemical evaluation of PD-L1 expression on tumor cells has become the most accepted predictive biomarker for PD-1/PD-L1 blocking therapies. It is generally accepted that high tumor expression of PD-L1 correlates with greater response rates, duration of response, and overall survival (44). However, a considerable proportion of PD-L1(–) patients experience substantial anti-tumor responses and significant differences in survival according to PD-L1 status have not been uniformly observed across all clinical trials. Hence, a universal acceptance and application of this marker remains controversial (42,45,51). In an attempt to further evaluate the prognostic value of PD-L1 expression, Aguiar and collaborators studied the records of 1979 patients with NSCLC enrolled in 13 clinical trials using Cochrane methodology (52). The investigators found a 29% response rate among 652 PD-L1(+) patients. In contrast, a 13% response rate was found among 915 patients with PD-L1(–) tumor samples (RR 2.08; 95% CI, 1.49–2.91; P<0.01). In addition to confirming an association between overall response rate (ORR) and PD-L1 status, there was an association with the intensity of PD-L1 expression independently of the immunohistochemistry assay utilized in the study (i.e., DAKO 28-8, VENTANA SP142, DAKO 22C3). The 24-week progression free survival was also evaluated in 6 of the studies included in the analysis. Among them, the ORR was 35% for 358 PD-L1(+) patients and 26% for 409 PD-L1(–) patients. This difference was also statistically significant (RR 0.79; 95% CI, 0.71–0.89; P<0.01). Interestingly, the 1-year survival rates were not different. The survival rate for 617 PD-L1(+) positive patients was 28% versus 27% for 779 PD-L1(–) patients. The heterogeneity of the groups was substantial and the difference did not reach statistical difference (RR 0.96; 95% CI, 0.87–1.06; P=0.39).

To add further complexity to the evaluation of PD-L1 expression as a biomarker, the biologicals currently under development have adopted different methodologies and cut-off points. An example of the conflicting preliminary results in this respect, is the FDA approval of nivolumab for the treatment of patients with metastatic NSCLC regardless of their PD-L1 status whereas the approval of pembrolizumab for the same patient population was limited to those with positive PD-L1 expression on their tumor tissues based on data submitted by the sponsor of the trial demonstrating superior efficacy among patients who expressed PD-L1 >50% using a tumor proportion score (53). Some of the challenges posed by this biomarker have been described and include: technical differences challenges related to assay performance, intra-tumoral heterogeneity of biomarker expression, and dynamic changes in PD-L1 expression related to previous therapies (51,54). Several groups of investigators continue to explore other biomarkers at a cellular (CD8+ T cells) and genomic (mismatch repairs in colorectal carcinoma) to be utilized alone or in combination with PD-L1 tumor expression (55).

Safety profile

The blockade of co-stimulatory receptors/ligands involved in inhibition of T cell activation is critical to overcome immunological tolerance. Therefore, it is intuitive to find a myriad of immune related adverse events associated with the safety profile associated with these agents. Moreover, these toxicities are of greater incidence and intensity in regimens combining checkpoint inhibitors such as an anti-CTLA4 antibody (ipilimumab) with PD-1 or PD-L1 antibodies (38).

Eigentler, Hassel, *et al*. comprehensively reviewed the safety profile and current recommendations for the treatment of immune related adverse events associated with PD-1 and PD-L1 blockade (56). Their manuscript is a comprehensive description of toxicities observed during the development of PD1 and PD-L1 inhibitors, and thoroughly visits each major group of endocrinopathies describing the time to presentation after treatment, their incidence in different clinical trials, and most importantly, the current treatment recommendations according to the type and severity of the adverse event.

For the most part, the toxicities associated with PD-1/PD-L1 inhibitors are grade 1 or 2 and easily manageable. Grade 3 or 4 toxicities are observed in approximately 1–3% of all patients. It is common practice to treat all grade 2 adverse events with corticosteroids (prednisone or methylprednisolone 1 mg/kg) until improvement to grade 1 or complete resolution. Therapy with the PD-1/PD-L1 inhibitor may continue thereafter once the steroids

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are tapered. Grade 3 or 4 toxicities also require systemic steroid therapy. However, on occasion, different types of adverse events may require higher doses of steroids, or the use of more potent immune suppressants. In these cases, and with the exception of hypothyroidism—in which thyroid supplementation is implemented, permanent discontinuation of the PD-1 inhibitor is recommended.

Discussion

The discovery of Immune checkpoint inhibitors constitutes the greatest historical advancement in the field of immunotherapy. Their importance is several folds. By renewing enthusiasm in the field of immunotherapy, immune checkpoint inhibitors have attracted major attention of researchers, clinicians, patients, and public in general. Such attention has resulted in large financial investments and established immuno-oncology as a solid field of cancer medicine.

Approximately ten different agents are being developed against different malignancies with promising preliminary results. The U.S. FDA has granted approval for five different tumor types including melanoma, NSCLC, renal cell carcinoma, bladder cancer, and Hodgkin's disease. Several other indications are in the process of completing their developing pathways and await or are under review by U.S. Federal authorities for approval. Current data available demonstrate improved safety and efficacy over selected traditional cytotoxics (43) and excellent efficacy in front line, or as second (39) or third line options (34) in different tumor types. Furthermore, fewer patients experience grade 3 or 4 toxicities when compared with traditional chemotherapy. In a majority of patients, toxicities are mild and manageable. Patients with moderate to severe toxicities require corticosteroids and their outcome is good for the most part (56). The development of other novel therapeutics with different mechanisms of action in immuno-oncology will rapidly demonstrate toxicity and safety signals allowing us to incorporate them to the management of patients with different types of solid and hematological malignancies. This rapid explosion of available options will soon lead to training programs in the field of immuno-oncology around the globe and accelerate future discoveries.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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