



Progress and Challenges in Precise Treatment of Tumors With PD-1/PD-L1 Blockade

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Immune checkpoint inhibitors target the inhibitory receptors on T cells to reinstate their antitumor ability and have shown significant efficacy in treating various cancers. However, because of tumor heterogeneity and many other uncover reasons, the objective response rate for programmed death 1 and programmed death-ligand 1 (PD-1/PD-L1) blockade is only 20 to 30%; its response rate in solid tumors is relatively low, and different degrees of side effects have occurred. There are still many unknown factors affecting the therapeutic effectiveness of PD-1/PD-L1 blockade. Additionally, screening the responding tumor patients accurately and improving the response rate and efficacy are huge challenges for tumor precise treatment. Here, we attempt to summarize the recent progress in response prediction and combined application of PD-1/PD-L1 blockade and briefly discuss the methods and evaluations combined with PD-1/PD-L1 blockade to improve the implementation of precision immunotherapy.

Keywords: PD-1, PD-L1, immunotherapy, patient response, precise treatment

OPEN ACCESS

Edited by:

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Specialty section:

This article was submitted to
Cancer Immunity and Immunotherapy,
a section of the journal
Frontiers in Immunology

Received: 25 October 2019

Accepted: 11 February 2020

Published: 12 March 2020

Citation:

Jiang Y, Zhao X, Fu J and Wang H
(2020) Progress and Challenges in
Precise Treatment of Tumors With
PD-1/PD-L1 Blockade.
Front. Immunol. 11:339.
doi: 10.3389/fimmu.2020.00339

INTRODUCTION

Immune checkpoint inhibitor (ICI) enhances effector T-cell function and has elicited long-term remission in patients with a broad spectrum of tumors. Over the past decade, ICIs have revolutionized the clinical management of advanced malignant tumors and dramatically changed the landscape of cancer treatments that rely heavily on radiotherapy, chemotherapy, and surgical resection. Programmed death 1 (PD-1) is expressed on activated T cells and negatively regulate T-cell responses, acting as a key checkpoint molecule in tumor-induced immune suppression; blockade of the interaction of PD-1 with its ligand, PD-L1 or PD-L2, has been shown to enhance the antitumor activity of T cells (1–4). Antibodies targeting PD-1/PD-L1 checkpoint stimulate the immune system to keep the tumor in check by releasing the immunosuppression. This strategy has emerged as a novel cancer therapy mechanism and plays an increasingly important role in the treatment of serious tumor types.

Although many patients with malignant tumors benefit from immunotherapy using PD-1/PD-L1 inhibitors, there are still no effective predictive biomarkers to guide the clinical precision medicine approach and clinical trial design at present. The research and identification of immunotherapy-related predictive indicators can promote tumor precise treatment and overcome drug resistance or adverse reactions. This review focuses on the recent progress in the efficacy

improvement of PD-1/PD-L1 inhibitors and the effective screening of patients to minimize the side effects. Herein, we summarized the biomarkers for predicting efficacy, common side effects and causes, and combination therapy strategies associated with PD-1/PD-L1 therapy.

RESPONSE PREDICTION AND INFLUENCING FACTORS OF PD-1/PD-L1 BLOCKADE TREATMENT

Gene Mutations

Genomic alterations in tumor cells correlate with tumorigenesis and response to anti-PD-1 therapy (5, 6). Tumor mutation burden (TMB) is an important indicator for evaluating the immunogenicity of tumors and an emerging biomarker for predicting the response to immunotherapy using cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1 checkpoint inhibitors (7–11). A correlation coefficient of 0.74 between TMB and anti-PD-1/PD-L1 immunotherapy response suggests that 55% of the differences in objective response rate (ORR) across cancer types may be explained by TMB (12). Although there may not be one universal definition of a high TMB, tumors with mismatch repair deficiency (MMR-d) and microsatellite instability (MSI) showed remarkable response to ICI therapy (6, 7, 13). Tumors with MMR-d can accumulate thousands of mutations by sequence alterations in the microsatellites, which render the tumors immunogenic and sensitive to ICI therapy (8). The US Food and Drug Administration (FDA) approved the use of pembrolizumab and nivolumab for the treatment of patients with advanced or metastatic solid tumors with MSI-high or MMR-d in 2017.

PD-1 Ligand Expression

Immune checkpoint inhibitors targeting the PD-1 axis include antibodies directed at PD-1, blocking receptor interaction with its ligands, PD-L1 and PD-L2 (1). Programmed death 1 ligand expression in solid tumors has been reported as a predictive biomarker of benefit from PD-1/PD-L1 axis inhibitors. Programmed death 1 ligand is highly expressed in various tumor cells and myeloid cells (14, 15), and multiple studies on a variety of tumor types have found the PD-L1 overexpression to be associated with ICI response (16–21). Conversely, other studies proved no such association (22, 23). The FDA has approved PD-L1 immunohistochemistry as a companion diagnostic indicator for anti-PD-1 therapy in patients with non-small cell lung cancer (NSCLC) (24–26). Programmed death 1 ligand on the tumor-derived exosomes released from some types of tumor is involved in the immune evasion of tumor cells (27–29). In the preclinical model of colorectal cancer, administration of PD-L1 antibody in combination with the inhibition of exosomal PD-L1 secretion could achieve tumor-suppressive effects (28). Exosomal PD-L1 is also a potential immunotherapeutic target that can address the current resistance to PD-L1 antibody therapy. The level of exosomal PD-L1 can indicate the level of T-cell activation by immunological checkpoint inhibitors and could be used as a prognostic marker (27). PD-L2, the other known ligand

of PD-1, positivity significantly predicted clinical response to pembrolizumab (30), while more studies are needed to determine the role of PD-L2 in PD-1 blockade treatment.

Heterogeneity of the Tumor Immune Microenvironment

The tumor microenvironment is a heterogeneous (31) and immunosuppressive environment composed of different cells and molecules (32, 33). The density, phenotype, and diversity of tumor-infiltrating lymphocytes (TILs) are crucial for ICI response (25). For some types of tumors, the level of TILs is a potential biomarker for ICI response (34). Many other immune cells may also affect the efficacy of anti-PD-1/PD-L1 therapy. The number of stimulatory dendritic cells (SDCs) in human melanoma can predict the patient's immune response and overall survival (OS), and SDC abundance is associated with the cytokines produced by lymphocytes, notably natural killer (NK) cells in human tumors (35). Therefore, the presence of NK cells in tumors is associated with an increase in the number of SDCs and the patient's long-term response to PD-1 antibody. Tumor-associated macrophages (TAMs) are associated with poor anti-PD-1 response in patients with melanoma (36). Although anti-PD-1 antibodies could initially bind to T cells as intended, the TAMs quickly removed these antibodies from T cells, thus inactivating them (37). In summary, a deeper understanding of the heterogeneity of the tumor immune microenvironment is essential to develop sensitive methods or potential predictive biomarkers for providing all the fingerprints of tumor microenvironment and then improve the efficacy of tumor immunotherapy.

Systemic Effects

Obesity

Obesity promotes tumorigenesis and progression associated with increased immunosuppression and potential side effects (38–42). Obesity was also shown to be associated with an increased efficacy of PD-1/PD-L1 blockade in both preclinical and clinical studies involving cancer patients (43). A retrospective study found the correlation between obesity and the efficacy of ICIs in cancer patients; ORR was significantly higher in the overweight/obese patients than in the non-overweight patients (44). Another study demonstrated that obesity is associated with increased efficacy of PD-L1 blockade in both tumor-bearing mice and clinical cancer patients (40). The preclinical trial on breast cancer found that fat cells overexpress PD-L1, affecting the therapeutic effectiveness and outcomes in breast cancer patients, and after inhibiting lipogenesis can selectively reduce the expression of PD-L1 in mouse adipose tissue and enhance the antitumor effect of PD-L1 or PD-1 antibody in a breast cancer model (40). Clinical studies have found that NSCLC patients with body mass index (BMI) ≥ 25 kg/m² have significantly reduced mortality after receiving the PD-L1 antibody treatment (especially in the case of high PD-L1 expression). However, analysis showed that treatment-related adverse events were not related to BMI (45). There may be other unknown factors affecting the response of obese patients to ICI treatment, such as the function and metabolic status of immune cells, which need to be studied further.

Gut Microbiome

Preclinical trials on murine models showed that the microbiome may influence the efficacy of some types of cancer treatment, particularly immunotherapy (46, 47). Researchers analyzing the fecal microbes in responding and non-responding melanoma patients undergoing anti-PD-1 immunotherapy found significant differences in the diversity and abundance of the gut microbiome in the two groups. Further analysis found that the intestinal bacteria in the responding patients' group enhanced systemic and antitumor immunity; meanwhile, germ-free mice receiving fecal transplants from responding patients achieved good tumor regression progress (48). These findings suggest that fecal transplantation may improve the efficacy of PD-1 and drug resistance-related issues in the future.

Neutrophil/Lymphocyte Ratio

Neutrophil-lymphocyte ratio (NLR) is a significant prognostic marker in many tumor therapies (49–53); high NLR indicates host inflammation and is associated with shorter OS in several tumor types (49). Comparisons of NLR before and after treatment with PD-1/PD-L1 inhibitors showed that patients with NLR ≥4 were found to have shorter OS and disease progression-free time before treatment (54). The NLR at 6 weeks after treatment initiation was a prognostic marker in patients with advanced NSCLC treated with anti-PD-1 antibody (55). These findings suggest that a high posttreatment NLR alone or its combination with other prognostic biomarkers can be useful indicators of OS and progression-free survival (PFS) in ICI treatment.

COMBINATION THERAPY STRATEGY

The three most common combination therapy strategies are PD-1/PD-L1 inhibitors in combination with CTLA-4 monoclonal antibodies (mAbs), chemotherapy, and targeted therapies (Table 1). There are four combination strategies approved by the FDA: two for kidney cancer [pembrolizumab (PD-1 antibody) plus axitinib (VEGFR/PDGFR inhibitor), and avelumab (PD-L1 antibody) plus axitinib], one for endometrial carcinoma [pembrolizumab plus lenvatinib (VEGFR/FGFR inhibitor)] and one for NSCLC (atezolizumab, bevacizumab, and chemotherapy) (57).

Combination With CTLA-4 mAbs

Cytotoxic T-lymphocyte-associated protein 4 was demonstrated to have a potent inhibitory role in Treg cell responses. Disruption of CTLA-4-CD80/CD86 interaction with anti-CTLA-4 antibody results in tumor rejection through enhancement of T-cell effector responses (58). The phase 3 trial CheckMate067 involving patients with advanced melanoma showed a significant improvement in ORR and OS in the nivolumab (PD-1 antibody) plus ipilimumab (CTLA-4 antibody) group; compared to CTLA-4 and PD-1 monotherapy, the risks of death in the combination therapy with the two drugs decreased by 46 and 35%, respectively. In the combination group, 21% of patients showed complete disappearance of the lesion and achieved complete remission, whereas 37% of the patients had 30%

TABLE 1 | Examples of clinical trials for combination therapy strategy.

Trial, phase (patient no.)	Condition or disease	Drug	Combination	Efficacy	Highest grade toxicities (%)	NCT (reference)
CheckMate-012 (phase I, n = 472)	Advanced NSCLC	Nivolumab	Ipilimumab, gemcitabine, cisplatin, pemetrexed, paclitaxel, carboplatin, bevacizumab, erlotinib	MPFS 12.7 months ORR 47 and 39%	Grade 3–4 adverse events were 42 and 31%	NCT01454102
CheckMate-067 (phase III, n = 1,296)	Unresectable or metastatic melanoma	Nivolumab	Ipilimumab	MPFS 11.5 months	Grade 3–4 adverse events 55% four treatment-related deaths: two in the combined group	NCT01844505
CheckMate-227 (Phase III, n = 2,220)	NSCLC	Nivolumab	Ipilimumab or nivolumab plus platinum doublet chemotherapy vs. platinum doublet chemotherapy	TBD	TBD	NCT02477826
Exploratory clinical study of apatinib and SHR-1210 in treating advanced hepatocellular carcinoma or gastric cancer (56) (phase I, n = 43)	Advanced HCC, GC/EGJC	SHR-1210 (anti-PD-1 antibody)	Apatinib (VEGFR2 inhibitor)	ORR 30.8%;	Dose-limiting toxicity events (26.7%); grade 3 lipase elevation (6.7%); grade 3 pneumonitis events (20%); grade ≥3 treatment-related adverse event 20 (60.6%); adverse events in ≥ 10% hypertension (15.2%)	NCT02942329
Keynote-426 (phase III, n = 429)	Renal cell carcinoma	Pembrolizumab	Axitinib, sunitinib	ORR 59.3%, PFS 15.1 months	Grade 3 or higher AEs 75.8%	NCT02853331
Keynote-021 (first-line, n = 123)	Advanced NSCLC	Pembrolizumab	Pemetrexed and carboplatin	ORR 56.7 vs. 30.2%	27% grade 3–5 treatment-related adverse events	NCT02039674

MPFS, median progression-free survival; AEs, adverse events; TBD, to be determined; AEs, adverse events; ORR, objective response rate; GC/EGJC, gastric or esophagogastric junction cancer.

reduction in lesions and achieved partial remission. However, 59% of patients in the combination group reported three to four adverse events (59). In the KEYNOTE-006 study, the 5-years survival rate was 38.7 and 31% in the Keytruda combination group and in ipilimumab monotherapy, respectively (60). The combination of two immunotherapies had a much better effect, but the cost of the treatment also increased, and so did the side effects.

Combination With Chemotherapy and Radiation

Preclinical research has suggested immunomodulatory properties for chemotherapy and irradiation (61). In 2018, the US FDA formally approved the PD-1 antibody Keytruda in combination with chemotherapy as the first line of treatment for NSCLC, regardless of the level of PD-L1 expression in patients, excluding patients with EGFR mutations and ALK fusion (62). Among the 616 patients, 410 patients received PD-1 combination therapy using Keytruda plus pemetrexed and platinum; the other 206 patients received chemotherapy with placebo plus pemetrexed and platinum. After 10.5 months of follow-up, the combination treatment group had an overwhelming advantage in all aspects. The ORR of the combined treatment group was as high as 47.6%, as compared to 18.9% in the chemotherapy group, and the combination treatment reduced the risk of disease progression by 48% (62). It is worth mentioning that regardless of the level of PD-L1 expression, the survival of patients in the combined treatment group was significantly prolonged. At the same time, many clinical trials of combination therapy with PD-1 inhibitors have yielded many exciting results.

Combination With Targeted Therapy

Targeted drugs have high efficiency but are susceptible to develop drug resistance. Therefore, targeted drugs in combination with ICIs may achieve high efficiency and long-lasting effect. The US FDA approved the PD-1 antibody Keytruda in combination with acitretin, an oral retinoid, for the treatment of patients with advanced renal cell carcinoma (63). This is the first PD-1 antibody and targeted combination therapy, officially leading to a new era of “immunity plus targeting” cancer treatment. Phase III clinical trial Keynote-426, which recruited patients with renal cell carcinoma from multiple countries around the world to more assess the efficacy of Keytruda in combination with axitinib, which is a second-generation tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3) (64). The ORR of the pembrolizumab–axitinib group was as high as 59.3%, whereas that of the sunitinib group was only 35.7%. Sunitinib is a small-molecule multitargeted receptor tyrosine kinase inhibitor. The PFS rates were 11.1 and 15.1 months in the sunitinib group and combination group, respectively, reducing the risk of death or progression by 31%. The 12-months survival rate was 89.9 and 78.3% for the combination group and sunitinib group, respectively, and the combination treatment group reduced the risk of death by 47% (65).

Side Effects and Resistance of PD-1/PD-L1 Blockade

An emerging challenge for PD-1/PD-L1 antibody therapy is the different levels of immune-related adverse events (irAEs), which include cardiotoxicity (66–68); cytokine release syndrome (69); myocarditis (70, 71); pneumonitis (72–74); hepatitis (74); thyroiditis (75, 76); endocrine dysfunction (77); fatigue, rash, and diarrhea (78, 79); and polymyalgia rheumatica/giant cell arteritis (80). Immune-related adverse events typically originate in the skin, gastrointestinal tract, liver, and endocrine system, although other organ systems may also be affected (81). Martins et al. (82) summarized the different types of irAEs and discussed the epidemiology and kinetics, risk factors, subtypes, pathophysiology, and screening and monitoring strategies for these adverse events and highlighted the important effects of managing irAEs. There are currently several guides on the management of irAEs (83–85).

Although immunotherapy is a long-acting method, it also develops resistance. After 21 months of follow-up in a study involving 205 patients with effective use of Keytruda, 74% of patients were still effective, whereas 26% developed resistance (86). Similarly, after a long-term follow-up of 42 patients with PD-1-effective malignant melanoma, 15 had developed resistance, and the resistance rate was 35% (87). CMP-001 (Checkmate Pharmaceuticals, Lianyungang, China), an investigational TLR9 agonist, could potentially mitigate this resistance, with an effective rate as high as 22%, including partial tumor disappearance (88).

In addition to FDA-approved methods, there are many potential discoveries that have yielded promising results in preclinical studies. Tumor necrosis factor (TNF) is upregulated in the intestine of patients suffering from colitis after dual ipilimumab and nivolumab immunotherapy. In the artificially induced mouse inflammatory bowel disease model, the anti-CTLA-4 and anti-PD-1 double treatment would aggravate inflammation. Prophylactic anti-TNF antibody or TNF inhibitor (TNFR2-immunoglobulin G) can significantly reduce the increased colitis caused by double-checkpoint blockade. Meanwhile, the authors found that TNF blockade could further enhance the infiltration of tumor-specific CD8⁺ T cells into the tumor microenvironment and draining lymph nodes caused by anti-PD-1 and anti-CTLA-4 monoclonal antibody combination therapy (89). A phase I investigator-initiated trial testing the safety of this combined approach is currently in progress.

CONCLUDING REMARKS

Programmed death 1/PD-L1 antibodies have become the standard treatment for more than 10 kinds of tumors. Currently, nine such antibodies have been approved for marketing worldwide, and still a large number of clinical trials are assessing the other therapeutic potential of PD-1/PD-L1 antibodies as a single drug or combination. The existence of individual heterogeneity has brought great difficulties to predict the prognosis or survival of patients treated with ICIs through a single diagnostic indicator. New markers

or groups that integrate multiple information are needed to predict the efficacy of anti-PD-1/PD-L1 immunotherapy. Immunotherapy requires real-time tracking of immune cells and evaluation of tumor responsiveness to immunotherapy by non-intrusive detection methods. Currently, researchers use biopsy or surgical resection of tumor samples for detection, but if relevant test factors can be found in the blood, it would be of great significance in determining the clinical effectiveness and responsiveness of immunotherapy. *In vitro* research models need to be closer to the state of the body, such as organoids incorporating the immune microenvironment (89, 90). Meanwhile, organoids can better reveal tumor progression and drug resistance and contribute to anticancer drug screening in the future (90).

Immunotherapy opens the way for precise treatment of malignant tumors. The current problems that ICIs need to overcome include accurate screening of sensitive populations, development of real-time dynamic monitoring of curative effects, accompanying diagnostic techniques and methods, development of high-throughput multimolecular multifactor integrated analysis methods, and sequential treatment. The key to improving PD-1 blockade therapy is the development of combination therapy, including other

checkpoints of the T cells or other immune cells, such as CTLA-4 and NKG2D (91). Further, molecular markers, including PD-L1, TMB, MSI, and TIL, need to be explored to guide clinical treatment. Next steps in immuno-oncology: enhancing antitumor effects through appropriate patient selection and rationally designed combination strategies. The application of single-cell sequencing technology reveals the heterogeneity of the tumor microenvironment and can help in the better understanding of tumor development and immune evasion.

AUTHOR CONTRIBUTIONS

YJ drafted the manuscript. XZ reviewed the manuscript structure and ideas. JF evaluated and reviewed manuscript structure, ideas, and science. HW conceived the topic and revised the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by National Natural Science Foundation of China (81872231) and Shanghai Committee of Science and Technology (2017YQ008).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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