Predictive Markers for Immune Checkpoint Inhibitors

Subjects: Oncology

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Immune checkpoint inhibitors (ICIs) have dramatically improved the outcomes of non-small cell lung cancer patients and have increased the possibility of long-term survival. However, few patients benefit from ICIs, and no predictive biomarkers other than tumor programmed cell death ligand 1 (PD-L1) expression have been established. Hence, the identification of biomarkers is an urgent issue.

Keywords: non-small cell lung cancer ; biomarker ; anti-programmed cell death ligand 1

1. Introduction

Lung cancer is the most frequent cause of cancer death worldwide. In 2020, 2.21 million new cases (11.4% of all cancer cases) and 1.80 million deaths (18.0% of all cancer deaths) were reported [1]. The most common histological type is non-small cell lung cancer (NSCLC), and most patients are diagnosed at an advanced stage [2]. Platinum-based chemotherapy has historically been the standard treatment for NSCLC, although limited therapeutic effects in patients with a poor prognosis have been observed. Recently, the advent of immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab (anti-programmed cell death 1 (PD-1) antibodies), atezolizumab and durvalumab (anti-programmed cell death ligand 1 (PD-L1) antibodies), and ipilimumab and tremelimumab (anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody) has dramatically altered the approach of advanced NSCLC treatment. First-line ICI therapy has demonstrated more prolonged survival than conventional platinum-based chemotherapy for stage IV NSCLC. In a phase III trial (KEYNOTE-024), pembrolizumab increased overall survival (OS) to 30 months for NSCLC patients with a PD-L1 tumor proportion score (TPS) > 50%, thereby demonstrating its superiority to conventional platinum-based chemotherapy [3]. Furthermore, a phase III trial (KEYNOTE-042) comparing pembrolizumab monotherapy with platinum-based combination therapy in NSCLC patients with PD-L1 TPS ≥ 1% showed significantly longer OS in the pembrolizumab group than in the chemotherapy group [4]. Atezolizumab also prolonged OS over platinum-based chemotherapy (17.5 vs. 15.1 months) in advanced NSCLC with PD-L1 ≥ 1% of tumor cells (TCs) or ≥ 1% of tumor-infiltrating immune cells (ICs), regardless of histology [5]. In a phase III study (CheckMate 227), nivolumab plus ipilimumab was associated with better OS than chemotherapy (17.1 vs. 14.9 months) in patients with NSCLC, regardless of PD-L1 expression level [6]. First-line ICIs combined with chemotherapy are among the current standard therapies for advanced NSCLC, compensating for the disadvantages of early treatment failure with ICI monotherapy. In a phase III trial (KEYNOTE-189) of patients with advanced NSCLC, the addition of pembrolizumab to platinum-doublet chemotherapy significantly prolonged PFS and OS (survival rate at 12 months was 69.2% vs. 49.4%) [7]. In addition, this combination therapy overcame the early failure of ICIs, which had been a problem with single-agent therapy [7]. In a phase III trial (KEYNOTE-407) evaluating the efficacy of pembrolizumab added to platinum-based combination therapy in patients with advanced lung squamous cell carcinoma (LUSC), OS was significantly prolonged (17.1 vs. 11.6 months) [8]. A phase III study (IMpower150) revealed that the addition of atezolizumab to carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab in non-squamous NSCLC patients significantly prolonged OS to 19.2 months [9]. Furthermore, in another phase III study (IMpower130), atezolizumab added to carboplatin/nab-paclitaxel significantly prolonged OS to 18.6 months [10], while in the CheckMate 9LA phase III trial, nivolumab/ipilimumab in combination with platinum-based therapy significantly prolonged OS to 15.6 months compared with platinum-based therapy in NSCLC patients [11]. ICIs also raised the possibility that advanced NSCLC patients may have a better chance of long-term survival. A first-line phase III immunotherapy trial (KEYNOTE-024) with pembrolizumab for NSCLC achieved a 5-year OS rate of 31.9% [12]. Two phase III trials of nivolumab (CheckMate 017 and CheckMate 057) in patients with previously treated advanced NSCLC demonstrated 5-year OS rates of 13.4% and 8.0%, respectively [13].

However, many NSCLC patients do not benefit from ICIs or suffer significant life-threatening immunotoxicity [14]. Immune-related adverse events (ir-AEs) can affect various organs, and dermatitis, pneumonitis, colitis, and endocrinopathies tend to be most common. While most cases are mild to moderate in severity, some cases are severe or even fatal, especially when not promptly recognized and appropriately managed [15][16]. Although it is essential to administer ICIs to appropriate

patients, the expression of programmed death-ligand 1 (PD-L1), a widely used biomarker, is not a sufficient predictive factor. ICIs are effective even in NSCLC patients with low or absent PD-L1 expression and may not be effective in patients with high PD-L1 expression. Therefore, there is an urgent need to identify new biomarkers to predict the response to ICIs for selecting the best anti-cancer agents for each patient.

2. Predictive Biomarkers beyond PD-L1 Expression

2.1. Tumor Mutational Burden

Tumor mutational burden (TMB) is defined by the number of mutation calls (somatic single variant (SNV) and multinucleotide variant (MNV) and small insertions and deletions (indels)) per megabase (Mb) of interrogated coding sequences. These mutations can be transcribed and translated into neoantigen-containing peptides, processed by the antigen-processing machinery, and loaded onto major histocompatibility complex (MHC) molecules for presentation on the cell surface. The immune system recognizes neoantigens as non-self-immunogenic targets, activating and targeting T cells [17][18][19][20]. Tissue and blood TMB is a potential biomarker of immunotherapy outcomes in multiple tumor types. In particular, lung cancer is primarily caused by chronic exposure to carcinogens in cigarette smoke, and the efficacy of ICIs correlates with a molecular signature characteristic of cigarette carcinogen-related mutagenesis, certain DNA repair mutations, and the burden of neoantigens [21][22]. An analysis of the CheckMate 568 study of nivolumab plus ipilimumab in NSCLC reported that ORR increased in patients with a higher tissue tumor mutational burden (tTMB) using the FoundationOne CDx (F1CDx) assay, plateaued at a threshold of 10 mutations (mut)/Mb (ORR: 4%, 10%, 44%, and 39% in patients with TMB <5, <10, 10, and ≥15 mut/Mb, respectively), and the enhanced response was independent of PD-L1 expression [23]. The CheckMate 227 study of nivolumab plus ipilimumab in NSCLC also demonstrated longer PFS in patients with tTMB-high, with at least 10 mut/Mb, irrespective of tumor PD-L1 expression level [24], while a phase III trial of durvalumab (MYSTIC) and tremelimumab indicated longer PFS and OS in NSCLC patients with blood TMB (bTMB)-high, with at least 20 mut/Mb [21]. A retrospective analysis of the POPLAR and OAK studies demonstrated that a positive correlation of tTMB and bTMB and NSCLC patients with bTMB ≥ 16 mut/Mb led to an increased PFS benefit from atezolizumab [25].

Although TMB is optimally calculated by whole-exome sequencing (WES), this approach presents difficulties in terms of its substantial cost and turnaround time in clinical settings [26]. To address this, targeted sequencing assays enriched with known cancer-driving gene mutations are used to assess TMB. The F1CDx assay and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay are moderately concordant with WES in TMB analysis [27][28], and both assays were recently approved as companion diagnostics by the FDA to assess TMB in solid tumors. In this approval, tTMB-high was defined as having at least 10 mut/Mb according to the KEYNOTE-158 study of pembrolizumab for unresectable or metastatic solid tumors [29]. Despite these initial positive findings, the role of TMB as a biomarker in NSCLC remains unclear. It was reported that tTMB was not predictive of the efficacy of pembrolizumab alone or in combination with chemotherapy according to retrospective analyses of the KEYNOTE-189 and KEYNOTE-021 studies, respectively [30][31].

TMB as a biomarker has other limitations, including a lack of standardization between the testing platforms. Low tumor purity may lead to inaccurate TMB estimates [32]. Lung cancer specimens often have a low tumor cell content due to inflammatory cells and stromal components, leading to an underestimation of TMB. Furthermore, although high-TMB is thought to lead to increased neoantigens, the effect on the tumor immune response may vary depending on whether the neoantigen is derived from clonal (or homogeneous tumor) or subclonal (or heterogeneous tumor) mutations because the lower antigen dosage compared with the clonal neoantigen burden reduces the chances of identifying T cells reactive to subclonal neoantigens. McGranahan et al. demonstrated that sensitivity to ICIs in NSCLC and melanoma patients was enhanced in tumors enriched for clonal neoantigens, and cytotoxic chemotherapy-induced subclonal neoantigens were enriched in certain poor responders [33].

2.2. DNA Mismatch Repair Deficiency and Microsatellite Instability

DNA mismatch repair (MMR) is a highly conserved biological DNA repair pathway in mammalian cells and is crucial for maintaining genomic stability. MMR deficiency (dMMR) is the initiating event in many cancer types [34]. The deficient DNA MMR mechanism leads to missed DNA replication errors, resulting in the increased acquisition of mutations, primarily in the form of microsatellite instability (MSI) or alterations in microsatellites, which increases the burden of neoantigens [35] [36].

A clinical trial of pembrolizumab across dMMR tumors spanning 12 cancer types demonstrated that ORR was 53%, and complete response (CR) was 21% [37]. This led to pan-cancer approval by the FDA. However, the role of the MMR status

as a predictive biomarker for immunotherapy in lung cancer remains unknown because it was not included in this study. The prevalence of MSI-high (MSI-H) status is rare, at 0.53% and 0.60% of lung adenocarcinomas (LUAD) and LUSCs, respectively [38].

2.3. CD8$^+$ Tumor-Infiltrating Lymphocytes

The adaptive immune system identifies and targets tumor cells. Interestingly, CD8$^+$ T cells, CD4$^+$ T cells, B cells, dendritic cells, and effectors of innate immunity, namely macrophages, polymorphonuclear leukocytes, and natural killer cells (NK), as well as all cell types within the tumor, are classified as tumor-infiltrating lymphocytes (TILs) [39][40]. Of them all, the presence of tumor-infiltrating CD8$^+$ T cells, which recognize tumor antigens, is a prerequisite for successful ICI treatment when presented at the tumor cell surface in the context of HLA class I. Several small-sized studies and a meta-analysis demonstrated that CD8$^+$ TILs were significantly associated with better OS, PFS, and ORR in NSCLC patients treated with ICIs [41][42][43][44][45][46][47]. Shirasawa et al. demonstrated a classification system based on PD-L1 expression and CD8$^+$ TIL status that accurately predicts the efficacy of ICIs in NSCLC patients better than tumor PD-L1 expression [48]. Furthermore, Kumagami et al. showed that the frequency of PD-1$^+$CD8$^+$ T cells relative to that of PD-1$^+$ regulatory T (Treg) cells in the tumor microenvironment could predict the efficacy of ICIs more accurately than tumor PD-L1 expression [49].

Although TILs have great predictive power, they present some technical problems as biomarkers in clinical practice, and CD8$^+$ TILs within the stroma and invasive margin compartment indicate a better outcome than those in the intratumoral compartment [45][50]. However, biopsy samples obtained by CT-guided needle biopsy or bronchoscopy in patients with advanced NSCLC are often insufficient to evaluate stromal TILs, and a sample may not represent the TME of the entire primary tumor or metastatic lesions.

2.4. Human Leukocyte Antigen Class I

The human leukocyte antigen (HLA) system encodes cell-surface proteins involved in immune system regulation [51]. Furthermore, HLA-I presents peptides derived from intracellular proteins on the surface of CD8$^+$ T cells, so that cancer cells are killed [52][53].

Several specific HLA-I genotypes are suggested as biomarkers for ICI treatment; Naranbhai et al. reported that HLA-A*03 alleles led to a low ORR and poor PFS and OS in various cancer patients, including NSCLC with ICI treatment, in the most significant epidemiological analysis of the association between HLA-I and ICI efficacy so far [54]. In melanoma patients, HLA-B44 supertype and HLA-A02 supertype led to prolonged OS with ICI treatment [55][56]. Losses in heterozygosity (LOH) and *HLA* gene expression have also been reported as candidate biomarkers. Chowell et al. reported that LOH in cancer reduces OS in NSCLC and melanoma patients with ICI treatment [55][56]. However, Negrao et al. reported no significant correlations between HLA-I zygosity and PFS or OS in NSCLC patients with ICI treatment [57]. Schaafsma et al. analyzed 33 cancer types and reported that tumors with high *HLA* gene expression tended to have higher immune cell infiltration, including CD8$^+$ T and NK cells, and a more immunologically active TME, thus leading to increased survival [58].

2.5. Blood Biomarkers

2.5.1. Peripheral T-Cell Phenotype

Surface and intracellular proteins expressed on T cells are expected to be biomarkers because ICIs target T-cell regulatory pathways. A prominent surface marker mainly expressed by CD8 effector memory T-cells is PD-1 [59]. Interestingly, PD-1 on CD8 TILs is used as a marker of tumor-reactive cells [60]. Indeed, peripheral blood PD-1$^+$CD8 T-cells can also express neo-antigen-recognizing T-cell receptors [61].

An analysis of 29 NSCLC patients treated with PD-1 inhibitor demonstrated that 70% of patients with disease progression lacked a PD-1$^+$CD8 T-cell response, whereas 80% of patients with a clinical response showed PD-1$^+$CD8 T-cell responses within 4 weeks from the induction of treatment Kamphorst et al. [62].

Furthermore, CX3C chemokine receptor 1 (CX3CR1) is a receptor of the chemokine CX3CL1, which is involved in the adhesion and migration of leukocytes [63][64]. Furthermore, CX3CR1 is a marker of T-cell differentiation and is rigidly expressed on CD8$^+$ T cells through irreversible differentiation from CX3CR1$^-$CD8$^+$ T cells during the effector phase [64][65], which theoretically provides an advantage as a biomarker compared with transiently expressed molecules on T cells. Yamaguchi et al. reported that an increase in the frequency of the CX3CR1$^+$ subset in circulating CD8$^+$ T cells early after ICI therapy correlated with response and survival in 36 NSCLC patients [66].

The $CD62L^{low}$ T-cell subpopulation in tumor-draining lymph nodes contains antitumor T cells and mediates potent antitumor activity when intravenously transferred [67][68]. Kgamu et al. reported that patients who responded to ICIs had a significantly higher ratio of effector $CD62L^{low}$ $CD4^+$ T cells in their peripheral blood before treatment, and that a decreased $CD62L^{low}$ $CD4^+$ T-cell ratio after ICI treatment resulted in resistance, with long-term survivors maintaining a high proportion of $CD62L^{low}$ $CD4^+$ T-cells [69].

2.5.2. Neutrophil-to-Lymphocyte Ratio

The neutrophil-to-lymphocyte ratio (NLR) is a surrogate marker of general host immune response to various stress stimuli. The systemic inflammatory response of cancer prompts neutrophil infiltration, resulting in the secretion of interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α (TNF-α), and vascular endothelial growth factor (VEGF) [70]. The activation and intratumoral invasion of lymphocytes are thought to be necessary for the antitumor activity of ICIs [71], while TNF-α and IL-10 cause lymphocyte dysfunction and a decrease in lymphocyte numbers [72][73].

2.5.3. Interferon-Gamma

Interferon-gamma (IFN-γ) is a cytokine that plays a role in innate and adaptive immunity, and is produced predominantly by T cells and NK cells for innate immunity but also by $CD4^+$ and $CD8^+$ T cells for adaptive immunity [74]. In tumors, TILs are the primary source of IFN-γ [75]. IFN-γ engages JAK/STAT signaling in the tumor cell, which induces MHC class I expression, accumulates effector cells, and promotes a loss of the suppressive activity of T-regs. Moreover, the deficiency of INF-γ inhibits effective innate and adaptive antitumor immunity [76][77].

Some reports suggested that a high-INF-γ level is related to the efficacy of ICIs. A study of durvalumab for previously treated NSCLC patients demonstrated that patients with a high pre-treatment IFN-γ signature (high levels of *IFN-γ*, *LAG3*, *CXCL9*, and *PD-L1* mRNA expression) had higher ORR, PFS, and OS [78]. An analysis of 17 NSCLC patients treated with nivolumab showed a trend of a more prolonged OS in those with high *INF-γ* expression compared with those with low *INF-γ* expression [79]. In the POPLAR study evaluating atezolizumab in NSCLC patients, a high T-effector-IFNγ-associated gene expression status was correlated with prolonged OS [80].

2.5.4. Interleukin-8

As is known, interleukin-8 (IL-8) is a member of the CXC chemokine family and was initially identified as a chemotactic factor for neutrophils [81]. Furthermore, IL-8 is secreted by malignant cells and tumor stroma cells across many different tumor types [82]. Moreover, IL-8 directly affects endothelial cells, malignant cells, and cancer stem cells, and indirectly affects attracting and modulating tumor-associated myeloid cells [83][84].

Sanmamed et al. reported early increases in serum IL-8 levels as a predictor of poor outcome in small retrospective cohorts of patients with advanced melanoma or NSCLC who received ICIs [85]. A retrospective analysis demonstrated that high levels of IL-8 at the initiation of ICIs led to a poorer OS across renal cell carcinoma, melanoma, NSCLC, and urothelial cancer [86]. However, a poorer OS was also observed for other factors aside from ICI treatment, suggesting that IL-8 may also be a prognostic marker rather than a predictive biomarker of ICI treatment.

2.5.5. Blood/Tissue Composite Biomarker

Nebet et al. demonstrated that pre-treatment circulating tumor DNA (ctDNA) and peripheral CD8 T cell levels are independently associated with the durable clinical benefit of ICIs, and developed the DIREct-Pre (durable immunotherapy response estimation by immune profiling and ctDNA pre-treatment) score system, combining tumor PD-L1 expression with pre-treatment ctDNA and circulating immune cell profiling [87]. Patients with higher DIREct-Pre scores had significantly longer PFS with ICIs [87].

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