Efficacy of PD-1 blockade therapy and T cell immunity in lung cancer patients

Hiroshi Kagamu and Kyoichi Kaira

Department of Respiratory Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan

ABSTRACT

Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1) or PD-1 ligand-1 (PD-L1) have brought paradigm shift in lung cancer treatment. The median overall survival of patients with advanced non-small cell lung cancer treated with former standard platinum doublet cytotoxic therapy is less than 1 year; however, patients responding to ICIs have durable antitumor efficacy resulting in survival longer than 5 years. Lung cancer has much gene mutations, which is a characteristic of cancer caused by extrinsic factors, such as cigarette smoking. The heterogeneity underlined by genetic mutations results in the generation of resistant clones against chemotherapy and molecular targeted therapy. On the other hand, gene mutation products generate neoepitopes that are recognized as ‘non-self’ by T cell immune system. This is one of the reasons lung cancer is a good target for ICIs. However, drastic antitumor response is observed in relatively small percentage of patients. The pre-existing T cell immunity required for PD-1 inhibitor to exhibit antitumor efficacy has been elucidated.

1. Introduction

Lung cancer is one of the malignancies with the worst prognosis. Platinum-based doublet chemotherapy, which has been the standard treatment for advanced lung cancer patients, can prolong survivals but merely for months. Epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors (TKI), and anaplastic lymphoma kinase (ALK)-TKI, targeting growth signals to which cancer cells addict by driver mutations, cause marked improvement in response rate; however, acquired resistance underlined by additional mutations and heterogeneity has never been avoidable. Thus, long-term survival of advanced lung cancer patients is hardly achieved with cytotoxic agents or TKIs that target cancer cells.

The cancer immune editing theory consisting of elimination phase, equilibrium phase, and escape phase, describes how tumor cells and immunity interact with each other [1–4]. Because every somatic cell is under immunological surveillance, which recognizes and eradicates the cells producing non-self gene products, the transformed cells presenting mutational products can be recognized by the immune system as non-self and be eradicated in the elimination phase. Sporadic cancer cells that somehow survive immune destruction may enter the equilibrium phase, in which cancer cell proliferation is under control by T cell immunity. T cells preferentially eradicate highly immunogenic clones that likely possess more mutations. Thus, during the equilibrium phase, not only number but also immunogenicity and mutational burden of cancer cells are edited. Conversely, T cell immunity is affected by long-lasting cancer cells, which attenuate its ability to control cancer cells. Immunologically sculpted cancer cells finally enter the escape phase, because of T cell immunity attenuation. Programmed cell death-1 (PD-1), which is known to mediate T cell exhaustion phenomenon of chronic viral infection models, plays a critical role in cancer antigen-mediated T cell suppression [5].

It has been demonstrated that PD-1 blockade therapy resulted in survival longer than 5 years in approximately 15% of advanced non-small cell lung cancer (NSCLC) patients [6]. Surprisingly, majority of 5-year survivors received only two year PD-1 blockade therapy without any further treatment in CA209-003 study. Thus, it appears that recovery of the equilibrium phase is possible with PD-1 blockade therapy even in advanced lung cancer patients. To improve the response rate and the probability of long-term survivals, T cell immunity components that are required for durable antitumor efficacy should be elucidated.

CONTACT Hiroshi Kagamu kagamu19@saitama-med.ac.jp

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2. Efficacy of PD-1 blockade therapy for NSCLC patients

In phase III clinical trials, nivolumab, an anti-PD-1 Ab, significantly improved overall survival (OS) in pretreated NSCLC patients compared to docetaxel [7,8]. The survival curves of nivolumab group showed no decline after a certain time point, and they were referred to as tail-plateau effect. Tail-plat-eau of PFS curves started 15–18 months after PD-1 blockade therapy. In other words, approximately half of the patients who had partial response (PR) or stable disease (SD) gradually acquired resistance and showed disease progression by 15–18 months after PD-1 blockade therapy (Figure 1). In contrast, clinical trial results consistently indicated that ~40% of NSCLC patients exhibited early disease progression in 3 months post-PD-1 blockade therapy. Thus, patients with NSCLC are classified into three distinct subgroups: non-responders showing early disease progression without clinical benefits, long-term survivors achieving durable disease control, and short-term responders. Pembrolizumab and atezolizumab have shown almost the same antitumor efficacy profile [9,10]. It is likely that pre-existing antitumor T cell immunity plays a critical role in determining these distinct outcomes after PD-1 blockade therapy.

3. Tumor PD-L1 expression and responses

The KEYNOTE024 phase III trial was conducted to compare pembrolizumab and platinum doublet chemotherapy in untreated NSCLC patients who had cancer cells with PD-L1 tumor proportion score (TPS) of 50% or greater [11]. Pembrolizumab significantly improved the overall response rate (ORR), progression free survival (PFS), and OS. The effect-iveness of pembrolizumab in TPS of more than 1% was later shown in the KEYNOTE042 trial [12]. These clinical trials provided evidence that PD-L1 expression in tumor cells have predictive significance for responses to pembrolizumab. However, it was demonstrated that cancer cells lacking PD-L1 expression by genome editing technique still responded to PD-1 blockade therapy [13]. In con-trast, PD-1 blockade therapy exhibited no antitumor efficacy in PD-L1 knockout mice, although the tumor cells expressed PD-L1. Thus, it is likely that PD-L1 expressed in the immune cells plays roles that are more crucial in the PD-1 dependent T cell suppression mechanism. It is well known that somatic cells including tumor cells express PD-L1 upon IFNγ exposure. The significance of tumor cell PD-L1 expression as biomarker likely reflects that T cell-mediated inflammation, which results in IFNγ production is important for antitumor T cell immunity.

4. Cancer antigen and responses

It has been demonstrated that cancers caused by extrinsic factors, such as lung cancer and melanoma, tend to respond well to ICIs, because they possess much mutational burden that is the source of cancer antigens. Neoepitopes generated from nonsynony-mous somatic mutations are recognized by the T cells as non-self, and are capable of evoking antitumor immune responses. However, all synonymous mutations do not equally generate immunogenic neoepitopes. To assess the immunogenicity of neoe-pitopes, fitness model was demonstrated [14]. In this model, two main factors determined neoantigen fitness: one is the likelihood of neoantigen presentation by the major histocompatibility complex (MHC) and the other is the differences from the original peptide sequence. The relative MHC bind-ing affinity of each neoantigen to its wild type and the nonlinear dependence on sequence similarity of neoantigens to known antigens provide these com-ponents. Low-fitness neoantigens predicted anti-PD-I responses in NSCLC patients. Similar observations were reported in renal cell carcinoma that insertion and deletion type mutations, which induced flame-shift type major sequence alterations and provided 3
times more neoepitopes with high MHC binding affinity, resulted in immunogenic antigens [15].

One more critical factor of somatic mutations as effective neoantigens is clonality. Transformation of a cancer cell is caused by accumulated gene alteration in one somatic cell. The mutations accumulated in the original cancer cell will be clonal mutation shared by all clones of cancer. Meanwhile, during proliferation of cancer cells, they acquire more mutations due to genetic instability. This type of mutation varies among cancer clones and mediates heterogeneity. N. McGranahan et al. [16] demonstrated that sensitivity to PD-1 blockade therapy in NSCLC patients was enhanced in tumors enriched with clonal neoantigens. Interestingly, subclonal neoantigens induced by chemotherapy were rich in certain poor responders. This observation is consistent with cancer immune editing theory. Because the elimination phase is supposed to begin very early when one somatic cell is transformed, T cells that mediate elimination phase likely recognize clonal neoantigens. During the equilibrium phase, the immunogenic cancer clones that possess more mutations are supposed to be preferentially eradicated. Thus, increase in subclonal mutations may reflect attenuation of antitumor T cell immunity. Indeed, melanoma study indicated that tumor mutation burden decreased in patients who responded to nivolumab but increased in PD patients [17].

5. T cell subsets mediating antitumor efficacy

5.1. CD8$^+$ T cell

It has been well established that CD8$^+$ T cells differentiate to acquire a state called cytotoxic T cells (CTL) that recognize MHC class I restricted antigen and induce cancer cell death. Thommen et al. [18] examined lung cancer tissue infiltrating lymphocytes and demonstrated that PD-1$^{\text{high}}$ CD8$^+$ T cells showed high clonality compared to PD-1$^{\text{med}}$ and PD-1$^{\text{low}}$ CD8$^+$ T cells in tumor microenvironment, and secreted IFN$^\gamma$ upon co-culture with cancer cells. Furthermore, PD-1$^{\text{high}}$ CD8$^+$ T cells correlated with favorable outcome of PD-1 blockade therapy. Tumor-infiltrating lymphocyte study also indicated that CD8$^+$ T cells, which recognized cancer antigens, appear to be the effector memory phenotype, which lacked CD62L but expressed CD45RO [19].

5.2. CD4$^+$ T cell

As indicated in cancer immune cycle model, priming and expansion of CTL that are specific for cancer antigens occur in lymph nodes draining antigen presenting cells (APC) from cancer tissues [20]. Thus, the potential rate-limiting steps include the priming and expansion of CTL and the trafficking from the lymph nodes to the tumors through the bloodstream. In line with this, the blockade of priming by MEK inhibition resulted in a loss of tumor infiltrating lymphocytes and memory T cells in mice [21].

Numerous evidences indicate that CD4$^+$ T cell help is necessary for priming, proliferation, migration and permeation abilities to tumor tissues, killing cell functions, metabolism, and survival of CTL [22]. Spitzer et al. [23] analyzed the tumors, the blood, the spleens, the bone marrow, and the draining lymph nodes to investigate the T cell clusters common in mice that established antitumor immunity sufficient to eradicate tumors, and reported that CD69$^+$CD44$^+$CD27$^-$CD62L$^{\text{low}}$T-bet$^+$ CD4$^+$ T cell cluster was the most valuable. This CD4$^+$ T cell cluster existed systemically. As a result, Wei et al. [24] analyzed melanoma-infiltrating lymphocytes, not only the exhaustion type PD-1$^+$ TIM-3$^+$ CD8$^+$ T cell but also ICOS$^+$ T-bet$^+$ type 1 helper (Th1) CD4$^+$ T cells were identified as antitumor T cell clusters. The CD4$^+$ T cell cluster in this study showed almost the same phenotype, ICOS$^+$CD69$^+$CD44$^+$CD27$^-$CD62L$^{\text{low}}$T-bet$^+$ CD4$^+$.
We reported that the percentage of CD62L<sup>low</sup> CD4<sup>+</sup> T cells in the peripheral blood before therapy predicted the outcome of PD-1 blockade therapy and correlated with the duration of responses in advanced NSCLC patients [25].

Summarily, exhausted-type memory effector CD8<sup>+</sup> T cells, and T-bet<sup>+</sup> Th1-like CD4<sup>+</sup> T cells are required for successful PD-1 blockade therapy (Figure 2).

6. Future directions
PD-1 blockade therapy for NSCLC is proceeding from monotherapy to combined therapy to achieve higher antitumor efficacy.

6.1. PD-1 blockade therapy and radiotherapy
Phase III PACIFIC trial was conducted to examine the efficacy of one-year durvalumab consolidation therapy after standard chemoradiation treatment for locally advanced NSCLC [26]. In comparison with placebo group, durvalumab therapy improved PFS and OS. Notably, the tail plateau of PFS curve was greatly improved with hazard ratio of 0.52; thus, it appears that one-year durvalumab therapy almost doubled the survival of patients requiring other treatment for long-term survival.

After having given radiation therapy, it is reported that the antitumor effect on tumor in the place apart from the irradiation field occurs and is called abscopal effect [27]. Immunogenic cancer cell death induced by irradiation therapy results in the activation of APC that engulf the cancer antigens in the presence of damage associated molecular patterns (DAMPs). The activated APC carrying cancer antigens migrate through the lymphatics to the draining lymph nodes, in which cancer antigen-specific effector T cells are primed and expanded by the APC. Thus, it is likely that radiotherapy can facilitate antitumor T cell priming, resulting in synergistic effects with ICI therapy, which promote antitumor efficacy of primed effector T cells. It was reported that prior radiotherapy improved the efficacy of PD-1 blockade therapy in NSCLC patients [28,29]. Interestingly, in the PACIFIC study, the hazard ratio was better in patients who started durvalumab therapy within 14 days after chemoradiation treatment, suggesting that T cell immunity augmentation by radiotherapy may have time limit.

6.2. Combined immunotherapy with anti-vascular endothelial growth factor (VEGF) antibody
IMpower150 study examined the antitumor efficacy of atezolizumab combined with bevacizumab, an anti-VEGF antibody and cytotoxic anticancer agents for untreated NSCLC patients [30]. OS and PFS were significantly improved by adding atezolizumab to CBDCA, paclitaxel, and bevacizumab. However, improvement in OS and PFS was not achieved by adding atezolizumab to CBDCA and paclitaxel in the absence of bevacizumab. This suggests the possibility that bevacizumab has synergistic antitumor effects with atezolizumab.

VEGF is one of the well-known immunosuppressive mediators. Myeloid derived suppressor cell (MDSC) and regulatory T cell (Treg) are known to express VEGF receptor2. VEGF activates and increases Treg and MDSC resulting in immune suppression. In addition, tumor vessels that are formed when there is high concentration of VEGF inhibit the migration and permeation of effector T cells into tumor tissues.

6.3. PD-1 blockade therapy and anti-CTLA-4 therapy
Phase III clinical trial Checkmate227 compared the antitumor efficacy of combination therapy of nivolumab and ipilimumab, an anti-CTLA-4 antibody and chemotherapy in untreated NSCLC patients [31]. OS and PFS were significantly better in the combination therapy group and showed higher tail plateau level indicating long-term survival effect. At first, the synergistic antitumor efficacy was prominent in patients who had high tumor mutational burden, but, later, the antitumor effect was shown in patients who had lower tumor mutational burden. As discussed in the former chapter, the potential rate-limiting steps of PD-1 blockade therapy include the priming and the expansion of T cells. Theoretically, CTLA-4 blockade can promote T cell priming, because CTLA-4 inhibits co-stimulatory signal of CD28, which is required for priming of naive T cells. Allison et al. reported that ipilimumab but not nivolumab alone caused increase in ICOS<sup>+</sup> Th1 CD4<sup>+</sup> T cells in the peripheral blood. In addition, Treg constitutively expresses CTLA-4 and some anti-CTLA-4 Ab have Treg removal effect; however, it is still controversial if ipilimumab can eradicate Treg in patients.

6.4. PD-1 blockade therapy and cytotoxic drugs
KEYNOTE189 and 407 studies examined the combination therapy effect of pembrolizumab and cytotoxic drugs in untreated NSCLC patients [32,33]. OS and PFS were improved by adding pembrolizumab to platinum doublet chemotherapy. The percentage of PD significantly decreased in patients who were treated with the combined therapy. Thus, it appears...
that combination of pembrolizumab and chemotherapy may eradicate different cancer clones each other, resulting in early additive effects. It has been reported that some cytotoxic agents could induce immunogenic cell death of cancer cells [34]. Thus, it is possible that cytotoxic agents have synergistic effects to promote antitumor T cell immunity. However, it is still uncertain if immunogenic cell death can promote T cell priming in patients treated with cytotoxic agents, because cytotoxic agents themselves and corticosteroid, which is used as an antiemetic agent, might damage APC and/or T cell functions. This concern must be further examined.

6.5. PD-1 blockade therapy for surgically resectable patients

Forde and colleagues reported that the use of neoadjuvant nivolumab was effective in resectable lung cancer patients [35]. A major pathological response was observed in 9 of 20 resected tumors (45%). Mutation-associated, neoantigen-specific T cell clones rapidly expanded in peripheral blood after nivolumab therapy in complete response patients. This result that early stage lung cancer patients possess antitumor effector T cells sufficient to eradicate cancer cells after nivolumab therapy is not surprising, because early stage patients likely entered the escape phase recently and are supposed to have more antitumor T cells without deep exhaustion than advanced cancer patients. It seems that resectable lung cancer patients can take this advantage with neoadjuvant PD-1 blockade therapy.

7. Conclusion

PD-1 blockade therapy has brought marked improvement in the outcome of lung cancer treatment. It is noteworthy that significant number of advanced lung cancer patients, who were treated with PD-1 blockade therapy, achieved long-term survival without disease progression. T cell clusters including CD8⁺ and CD4⁺ cells required for successful ICI therapy have been elucidated. Comprehensive understanding of T cell immunity and precise analysis of factors that prevent the equilibrium phase will provide adequate treatment of lung cancer patients, resulting in immune precision medicine.

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