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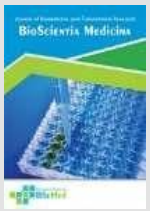

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Immunotherapy in Lung Cancer: A Narrative Literature Review

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A B S T R A C T

Lung cancer is the most common cause of death from cancer in both men and women worldwide. Cancers with low immunogenicity often do not present antigens, so immune responses can be avoided. Uncontrolled growth of tumor cells occurs due to various factors such as activation of immunosuppressive mechanisms, induction of various immunosuppressive cells, and expression of immune checkpoint molecules. The development of lung cancer management has progressed since the discovery of molecular-based target therapy and immunotherapy. The high expression of tumor mutational burden in lung cancer indicates high immunogenicity in lung cancer. Various immunological mechanisms involving programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) have been developed for the treatment of lung cancer by utilizing immune system modulation. Nivolumab is the first approved immunotherapy for lung cancer, followed by pembrolizumab, atezolizumab, and durvalumab. The use of immunotherapy involving immune checkpoint inhibitors is an important breakthrough in the management of cancer, including lung cancer. This literature review aimed to describe immunotherapy in lung cancer that focuses on immune checkpoint inhibitors anti-PD-1 and anti-PD-L1.

1. Introduction

Lung cancer incidence globally by sex ranks first in men and ranks third in women. Globocan in 2020 reported that in Indonesia, lung cancer ranks first in cancer deaths.[1] The high mortality rate for lung cancer is caused by non-specific complaints, making it difficult to establish a diagnosis at an early stage. About 57% are malignant and can attack various tissues and organs.[1,2]

Lung cancer is divided into two based on cell type, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell Lung cancer is the most common type of lung cancer, accounting for 80-85% of total lung cancer cases. NSCLC is known as a tumor that grows slowly before eventually becoming malignant and spreading to the surrounding organs and tissues. According to research, only 5% of NSCLC patients with advanced stages survive, even though currently, there are many choices of therapeutic modalities. Small cell carcinoma lung cancer grows quickly and is found more often in smokers than nonsmokers.[2] Molecular examination of lung cancer patients is an important thing to do to provide specific and personalized management. Molecular markers that are commonly used are epidermal growth factor receptor (EGFR) tests, anaplastic lymphoma kinase (ALK) rearrangement, and programmed death ligand-1 (PDL-1) expression.[3]

Immunotherapy has been used for several years to treat various types of cancer, but not for lung cancer. Lung cancer was previously believed to be a non-immunogenic disease, so it did not cause a significant immune response. Lung cancer cells have the ability to evade and suppress the immune response by

changing the activity of cytotoxic T lymphocyte cells. The immune response has various elements that can be used as markers and predictive factors for the administration of immunotherapy. Recent technological developments have helped the understanding of immune system regulation in lung cancer resulting in immunotherapy.[3,4] The high expression of tumor mutational burden (TMB) in lung cancer indicates high immunogenicity in lung cancer. Immunotherapy is expected to have a good response to the management of lung cancer.[5] This literature review aimed to describe immunotherapy in lung cancer that focuses on immune checkpoint inhibitors anti-PD-1 and anti-PD-L1.

Cancer immunology

Immune cells that play an important role in immuno-oncology include the cytotoxic T-cell group. T cells have the most important role in the identification of tumor cell antigens. T cells differentiate into two subtypes, namely T-helper 1 (Th1) cells and T-helper 2 cells. (Th2). Th1 cells have effectors in the form of macrophages and CD8+, while Th2 cells have effectors, including B cells, eosinophils, basophils, and mast cells.[3,4]

Cancer cells can regulate the immune system so that they can escape surveillance by the immune system. The immune system can recognize neoantigen-expressing new tumor cells and eliminate cells to maintain tissue homeostasis in complex multicellular organisms. This process in lung cancer is a complex process and decreases with the severity of the disease.[6,7] Immunosurveillance is the control of the immune system by the body. Tumor cells can still develop in a body with a good immune system, even though the immunosurveillance mechanism is running. This mechanism of avoiding the immune system by tumor cells is known as immunoediting or immunoediting role in the process of malignancy formation.[8,9]

Immunoediting consists of three phases, namely elimination, equilibrium, and escape. The elimination phase is the phase of the innate and adaptive immune response in eradicating growing tumor cells and consists of four stages. First, recognition and limited elimination of tumor cells by innate immune cells. Second, APC maturation and migration and antigen presentation to T cells. Third, the formation of tumor cell antigen-specific T cells and activation of cytotoxic mechanisms. Fourth, the return of tumor cell antigen-specific T cells to the tumor site and elimination of tumor cells. In the elimination phase, immune cells that play a role include NK cells, macrophages, dendritic cells, CD4+, and CD8+. In general, the elimination phase occurs when the immune system recognizes abnormal cell growth and induces apoptosis in these cells. Not all tumor cells are eliminated in this phase. Some tumor cells can survive and progress to the next phase.[3,8]

The equilibrium phase is a continuation of the elimination phase. The reduction of the immune system in the equilibrium phase makes the growth of tumor cells stagnate due to the restriction of the remaining immune system. Tumor cells continue to grow, but there has been a selection of tumor cells that have low immunogenic properties so that various tumor cells that are resistant to the immune system are formed. Surviving tumor cells experience a state of slow productivity and long latency. The equilibrium phase is a phase with a long time span so that dormant tumor cells can experience various changes, such as deoxyribonucleic acid (DNA) mutations or gene expression that creates variants of tumor cells with different mutations that cause a more severe state of resistance.[8]

The escape phase is a stage where tumor cells can display and mimic normal cell mechanisms so that they can avoid induction of apoptosis and become malignant cells. The escape phase occurs when some tumor cells that are resistant to immune cells manage to escape the editing mechanism. This situation occurs due to genetic and epigenetic changes that make tumor cells have three conditions to evade the immune system. First, the reduction in the process of recognizing tumor cell antigens due to changes in tumor cells or effector cells. Second, avoid cell death.

Third, the release of various pro-tumorigenic factors by tumor-associated stromal cells (TASC), such as vascular endothelial growth factor (VEGF), IL-6, IL-8, and others that cause immunological tolerance.[8]

Tumor cells can also evade the immune system by mechanisms that can cause tumor cells to grow uncontrollably and form clinically detectable lesions. Tumor cells can reduce their immunogenicity by reducing the expression of antigens, costimulatory molecules, and MHC, which function in activating the immune response. Tumor cells cannot be recognized by the immune system because tumor cells can transfer antigens on their surface into the cytoplasm, which makes the immune system unable to recognize tumor cells as foreign.[8,9]

The ability of tumor cells to paralyze various components of cytotoxic immune cells through the release of factors or the recruitment of immunosuppressive inflammatory cells. This situation is indirectly created in the tumor microenvironment through the secretion of various mediators that can inhibit effector cell function and immune cell development, such as IL-10, transforming growth factor-β (TGF-β), tumor necrosis factor (TNF), and VEGF. This state can be induced through the activation of regulatory T cells (Treg) dan myeloid-derived suppressor cells (MDSC).[9]

The high expression of tumor mutational burden (TMB) in lung cancer indicates high immunogenicity in lung cancer. High TMB will cause mutations in tumor cells. These mutations produce neoantigens on the surface of tumor cells. The higher the TMB, the higher the mutations in tumor cells, which will result in more neoantigens being produced by tumor cells. This opportunity is used for immune cells to recognize tumor cells. This hope underlies the provision of immunotherapy for lung cancer.[5]

Immune checkpoint molecules

T cell activation at least requires signaling through three mechanisms, namely TCR binding with MHCI, costimulatory molecule signals, and cytokines. Costimulators and co-inhibitory molecules are included in the immune checkpoint class, which work in regulating the immune response. Inhibitor molecules function to inhibit the overactivity of T cells and tolerate the immune system, while costimulatory molecules do the opposite. Basis of immunotherapy in the management of lung cancer by inhibiting the immune checkpoint.[3]

Programmed death-1 (PD-1) dan programmed death ligand-1 (PD-L1)

Tumor cells evade attack by cytotoxic T cells by decreasing the expression of antigens and costimulatory molecules. Another factor that also plays a role in immunoediting is the regulation of anti-cancer responses from immune cells, such as inhibition of CTL activity due to the expression of programmed death receptor 1 (PD-1). The PD-1 molecule (CD279) is an immune checkpoint that is expressed on various types of immune cells such as T cells, B cells, monocytes, dendritic cells, and tumor-infiltrating lymphocytes (TILs). The ligand is programmed death ligand 1 (PD-L1) is expressed on tumor cells and antigen-presenting cells (APC).[10]

The interaction of PD-1 and PD-L1 is normally a response to various degrees of inflammation at sites that express antigens to prevent tissue damage. When T cells recognize antigens expressed by MHCI on APCs or on the surface of tumor cells, they produce proinflammatory cytokines and initiate a series of inflammatory processes. Proinflammatory cytokines will induce PD-L1 expression in surrounding tissues and activate PD-1 protein on the surface of T cells. The interaction of PD-1 and PD-L1 results in tolerance of the immune system, namely the inability to trigger T cell activation and inflammatory response even when antigen is present.[10]

There are two types of PD-1 ligands, namely PD-L1 (B7-H1) and PD-L2 (B7-DC), but only PD-L1 has an effect on the modulation of the immune system. PD-L1 expression in several types of tumors occurs in large quantities so that the immune response against the tumor can be avoided. PD-L1 expression in tumor cells and hematopoietic cells is determined by the

stimulation of proinflammatory cytokines such as IFN-γ and TNF-α. Increased PD-L1 ligand expression is a potential biomarker for NSCLC. The interaction of the PD-L1 ligand on tumor cells with the PD-1 receptor on T cells will lead to a significant decrease in tumor-specific T-cell production and proliferation and affect cytokine production, thereby reducing the number of active immune cells in the blood. This interaction also causes tumor cells to be spared from the process of elimination mediated by CD8+. Blockade of PD-1 or PD-L1 molecules with monoclonal antibodies can block this interaction, thereby providing a protective immune response to kill tumor cells.[4,10]

In the early stages of the immune response, the regulation of T cell proliferation is influenced by CTLA-4, while in the advanced stages, decreased T cell activity is affected by PD-1, especially in peripheral lymph nodes. T cell activation is generally mediated by stimulation of TCR receptors on T cells by MHCI-presented antigens on APCs or tumor cells as well as binding of the costimulator molecule CD28 on T cells to B7 ligand on APC. TCR stimulation without binding to the costimulator molecule will only make T cells enter a non-responsive state. Inhibition of T cell activity is mediated by stimulation of the PD-1 receptor on T cells by PD-L1 ligands on APC or tumor cells. Stimulation of the CTLA-4 receptor on T cells by the B7 ligand on APC can also inhibit T cell activation. This is used to increase the aggressiveness of the immune response against cancer cells. CTLA-4 and PD-1 can inhibit T cell activation through a synergistic mechanism.[10]

Immunotherapy has recently been developed to inhibit tumor cell-induced immunosuppression, including monoclonal antibodies against PD-1, PD-L1, and CTLA-4. Monoclonal antibodies are antibodies that act on immune checkpoint molecules so that it can inhibit the interaction of PD-1 and PD-L1. Inhibition of PD-1 or PD-L1 can interfere with the immune checkpoint. This is so that T cells will be activated and carry out their functions in the recognition and elimination of tumor cells. Anti-PD-1 and anti-PD-L1 can selectively target and restore immune responses in the tumor microenvironment. Antibodies against PD-1 that have been shown to provide benefits in lung cancer include pembrolizumab and nivolumab, while antibodies against PD-L1 include atezolizumab and durvalumab.[11]

Immunotherapy for non-small cell lung cancer (NSCLC)

Immunotherapy in NSCLC, based on immune checkpoint inhibitors (ICI), recommends first-line and second-line therapy. Outcomes that are considered in the use of therapy are; overall survival (OS), objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR).[12] Firstline ICI immunotherapy in NSCLC is used as monotherapy if PD-L1 expression is ≥50% without driver mutations in patients or as a combination of platinum-based chemotherapy. Whereas for PD-L1 expression <50%, it is recommended to use a combination of ICI with doubled platinum-based chemotherapy.[13] The ICI agents of choice on several grounds are anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (atezolizumab, durvalumab). There are several things that must be considered regarding contraindications, including; autoimmune disease, allergy to immunotherapy, and patient performance status >1.[13]

The target of immunotherapy in lung cancer is not only targeting the PD-1 receptor, but also the PD-L1 ligand. One example of anti-PD-L1 is atezolizumab which is a humanized IgG1 monoclonal antibody. Atezolizumab is a monoclonal antibody that binds to PD-L1, thereby inhibiting the interaction of PD-L1 with PD-1 and PD-L1 with B7.1 (CD80).[14,15] Administration of atezolizumab monotherapy compared to chemotherapy has been studied in the Impower110 study as the first line of NSCLC treatment stage advanced, chemotherapy-naive, without EGFR or ALK mutations. The atezolizumab group with high PD-L1 expression experienced a median OS of 7.1 months longer than the chemotherapy group (20.2 months vs 13.1 months). The median PFS in the atezolizumab group was 8.1 months, while that in the chemotherapy

group was 5.0 months. The toxicity of the drug did not change when compared to previous studies. Grade 3 or grade 4 adverse events occurred in 30.1% of subjects in the atezolizumab group and 52.5% of subjects in the chemotherapy group. The most frequently reported side effects include anemia, neutropenia, and thrombocytopenia.[13,16]

Immunotherapy for small cell lung cancer (SCLC)

Many SCLC patients come with extensive stages, and the prognosis is poor. In recent years, immunotherapy has demonstrated clinical activity against the SCLC stage extensively, although much research is still ongoing. The addition of atezolizumab to the standard chemotherapy regimen reduced the risk of death by 30% and increased the median OS by two months (12.3 months vs. 10.3 months; HR 0.70, p=0.007). The 1-year survival in the atezolizumab group compared to the placebo was 51.7% vs. 38.2%. The median PFS in the two groups was 5.2 months and 4.3 months, respectively (HR 0.77, p=0.02). An exploratory analysis of 351 (93.8%) samples that underwent TMB examination found that the clinical benefit of adding atezolizumab was mainly found in the group with TMB ≥10 mutations/MB.[17]

Immunotherapy side effects

Side effects caused by immunotherapy have different degrees and types. There are five types of side effect degrees according to the common terminology criteria for adverse events (CTCAE), which has 5 degrees, from mild 1st degree to 5th degree, which causes death due to side effects.[18] The side effects caused by ICI depend on the immune checkpoint that is the target. Immune-related adverse events or immune-related adverse events (irAEs) are common in skin, gastrointestinal, endocrine, liver, and lung organs. Skin reactions are the most common side effect in patients receiving ICI PD-1 and CTLA-4 and usually occur within the first few weeks of treatment. Severe skin reactions are rare. Skin rash was reported to occur in approximately 15% of the anti-PD-1 group and 24% in the anti-CTLA-4 group.[19] Diarrhea and colitis are more common on anti-CTLA-4 than on anti-PD-1, with grades 3-4 occurring in 1-2% of cases. Colitis is one of the most common immune-related side effects, with approximately 5% occurring with anti-PD-1 and anti-PD-L1 and 25% with anti-CTLA-4. Patients usually complain of diarrhea, abdominal pain, or gastrointestinal bleeding. Stool analysis and abdominal CT scan with contrast can be performed to assess the intestinal thickening that is characteristic of colitis. Patients with strong clinical features of colitis should be managed with high doses of steroids while awaiting colonoscopy. Grade 1 treatment usually requires conservative management in the form of hydration and anti-diarrheal drugs. Grades 2-3 should be considered discontinuing ICI administration until conversion to grade 1 occurs.[19,20]

Pneumonitis was more common in combination immunotherapy than in monotherapy (10% vs 3%). Pneumonitis occurred in 72% of cases as a grade 1-2 side effect, and symptom improvement occurred in 86% of cases after delaying ICI administration. Pneumonitis can occur from the 9th week of treatment with atypical symptoms, namely dry cough, shortness of breath, cyanosis, and fatigue. Pneumonitis caused by ICI radiologically gives a picture of extensive inflammation in the lung parenchyma. Delay in establishing the diagnosis of pneumonitis can result in chronic and irreversible lung damage. Radiological evaluation with CT scans every three or four weeks should be performed in any degree of pneumonitis to assess progression. For side effects of grade 4 pneumonitis, ICI administration must be stopped, then given empiric antibiotics, prednisone for 4-6 weeks as well as bronchoscopy and bronchoalveolar lavage (BAL).[19,20]

Evaluation of immunotherapy in lung cancer

Immunotherapy evaluation used immune-based therapeutics response evaluation in solid tumors 1.1 (iRECIST 1.1), which is a modification of RECIST 1.1. Immunotherapeutic agents induced differences in tumor response when compared to standard chemotherapeutic agents. The positive effects of

immunotherapy have been proven in the treatment of lung and other cancers. Apart from its positive effects, immunotherapy may display atypical response patterns, such as delayed tumor size reduction, mixed response, or even increased tumor burden at the start of therapy due to the increasing size of the lesion and/or the incidence of detecting new tumor lesions which are then followed by a gradual decrease in tumor burden. Gradually, this occurrence is referred to as pseudoprogression.[21]

Response evaluation in solid tumors 1.1 failed to recognize the pseudoprogression potential and long-term effectiveness of immunotherapy because significant tumor enlargement and/or newly detected tumor lesions would be classified as progressive disease (PD), according to RECIST 1.1. Incorrect therapy termination decisions and inappropriate patient exclusion in clinical studies. There are two assessments, namely baseline evaluation, and follow-up. Baseline evaluation is the measurement of baseline data that should be carried out as close as possible to the time when immunotherapy was started.[21]

Regular follow-up every 6-12 weeks is recommended for iRECIST. Follow-up monitoring is consistent with RECIST 1.1, all target lesions selected at baseline measurements should be re-measured quantitatively, and all non-target lesions should be evaluated qualitatively. A target lesion that has been selected on the baseline measurement will still be categorized as a target lesion even if it is reduced to below 10 mm on subsequent measurements, and vice versa is a non-target lesion, and this is valid until the completion of a treatment regimen.[21]

2. Conclusion

PD-L1 expression ≥50% without any mutation drivers can make immunotherapy monotherapy or a combination of concomitant immunotherapy with platinum-based chemotherapy the first line for NSCLC. In comparison, PD-L1 expression of 1-49% makes immunotherapy the first line by being given in combination with platinum-based chemotherapy.

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